2706

JPRS: 2706

24 June 1960

MEDITSINSKAYA RADIOLOGIYA
[Medical Radiology]

No 9

1959

Distributed by

OFFICE OF TECHNICAL SERVICES
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205 EAST 42nd STREET, SUITE 300
NEW YORK 17, N. Y.

JPRS: 2706

CSO: 3434-N

MEDITSINSKAYA RADIOLOGIYA

[The following are full translations of selected articles in Meditsinskaya Radiologiya (Medical Radiology), Vol IV, No 9, pages 13-17, 24-28, 66-90.]

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ANNALS

Changes in the Conditioned Reflex Activity of the Offspring of Dogs Which Have Been Subjected to Chronic Irradiation With Sr^{90}

V. A. Nazarov

I. V. Sanotskiy, S. P. Voskresenskiy and A. P. Novikova, T. A. Ivanova, N. G. Trusova and others in experiments on animals have established the fact that internal irradiation associated with the entrance of radioactive isotopes into the bodies of the parents even in small quantities produces changes in the development of the offspring and a reduced viability of it. These investigations, however, did not deal with changes in the condition of the nervous system of the offspring of the irradiated animals.

We have already reported on the results of investigation of dogs the parents of which had been given a mixture of uranium fission products in the food, a mixture which contained 24.1 percent Sr^{90} and which was given once according to the calculation of one mC°kg. In the study of the conditioned reflex activity of the adult offspring of irradiated dogs a marked weakening of the associative function and a reduction in the functional capacity of the cerebral cortex were detected. In these dogs an increase level of electrical activity of the cerebral cortex was observed with a predominence of relatively fast rhythms, paradoxical reaction to light stimuli of different strengths (method of "curve reactivity") and increase in the after-induction. The data obtained indicate a notable weakening in the strength and mobility of the nervous processes in the offspring of irradiated dogs.

In the present report we have the opportunity of evaluating the results of similar observations made in five adult (one and a half-two years) dogs the parents of which (mother and father) had sustained chronic internal irradiation with the β-rays of Sr^{90} for 17-28 months.

The Sr^{90} was introduced into the food every day according to the calculation of 0.2 and 0.02 microcuries/kilogram per day. The introduction of Sr^{90} into female animals was completed at the time of delivery. The quantity of Sr^{90} introduced into the body of the mother throughout the entire period of irradiation was equal to eight microcuries/kilogram (in two cases) and 90 microcuries/kilograms (in one case). The tissue doses in the mother as determined in the skeleton amounted, respectively, to 90, 230, and 600 rad at the time of delivery.

The examination of the conditioned-reflex activity

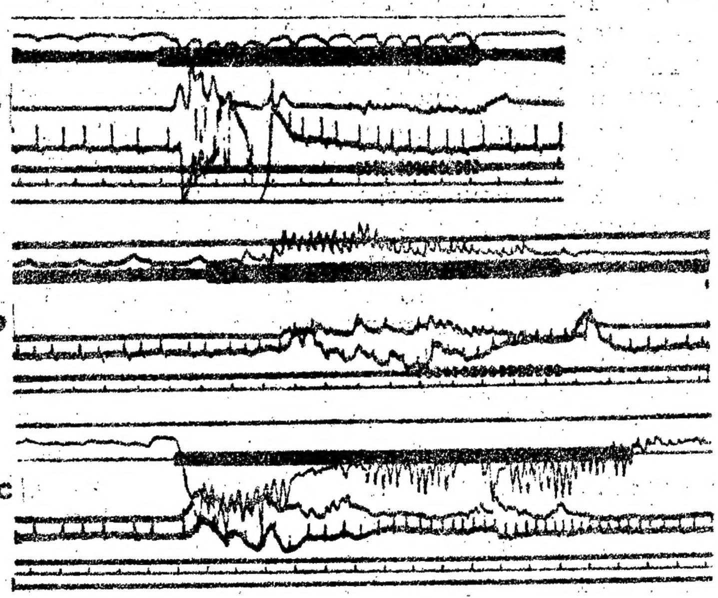
was accomplished after a preliminary adaptation of the dogs to the chamber and to their stalls. Five dogs served as controls; they were about two years of age and born of irradiated animals. Defense conditioned reflexes were formed to sound and light stimuli (bell, buzzer, interrupted GZ-1 and flickering light signals). Electrocutaneous stimulation of the hind extremity with an induction current was used as the reinforcement; the circuit of the induction coil was broken synchronously with rhythmical sound and light signals (the movement of the extremity was recorded by the electrical method on photographic paper simultaneously with an electrocardiogram and a pneumogram by means of an elastic carbon feeler attached to the leg). The magnitude of the conditioned reflex motor response was evaluated according to the degree of deviation of the "light beam." The experiments were carried out every other day. In every experiment there were five to eight combinations with intervals of three to five minutes.

The offspring of the chronically irradiated dogs examined had an entirely healthy appearance and a normal state of nutrition. The examination did not reveal any difficulties in the formation of the defense conditioned reflexes. The first appearance of the reflex to a stimulus of moderate strength (buzzer) occurred with subsequent reinforcements: in the control group, in the 16th, 21st, 22nd, 24th and 27th; on the average, with the 22nd reinforcement; in the experimental group, in the sixth (600 rad), ninth (230 rad), 14th (230 rad), 16th (90 rad) and 19th (90 rad), and, on the average, with the 13th reinforcement. (Tissue doses determined in the bone tissue of mothers are given within the parenthesis).

Therefore, the conditioned reflex was elaborated in experimental dogs even somewhat more quickly than in the control animals, and the reflex appeared earlier the greater the tissue dose received by the parents. The consolidation of the reflex in the experimental animals occurred quite quickly and practically no omissions of it were observed (except for special tests).

The subsequent reflexes were also elaborated rapidly and surely, without any disturbance in the strength relationships. At the same time, it was established that the stimulatory process associated with a realization of the conditioned association which occurred usually was expressed in the offspring of irradiated dogs in an excessive and inadequate form, being expressed in a general excitation of the animal. As a rule, the dogs which had stood calmly in the stall before this began to react to the stimulus as early

as the first appearance of the conditioned reflex (buzzer, flickering light) with yelping, barking, attempts to free themselves from their straps, etc. Here, an increased mobility of the vegetative reactions was characteristic: a notable increase in frequency in the pulse (from 80 to 120 beats a minute or more) and an exceptionally marked increase in respiratory rate -- from 20-30 to 220, that is, up to the frequency of the induction current shocks which served as the reinforcement. This effect was rapidly consolidated, occurring in the second-third second of the effect of the conditioned stimulus (both rhythmical and interrupted), and terminated immediately after it was switched off (see figure b).



Electrograms. Course of Defensive Conditioned Reflex Reaction to A Stimulus of Moderate Strength (Buzzer) in Dogs of Control and Experimental Groups. From above down: respiration, conditioned stimulus (buzzer); movement of the extremity -- conditioned and unconditioned reactions; electrocardiogram; record of unconditioned (electrocutaneous) stimulus (frequency of induction current shock -- about three, seven per second or about 220 per minute); record of time (one-second intervals).

a -- control; the motor conditioned reflex reaction is seen as well as a moderate increase in the respiratory and pulse rate against a background of the effect of the conditioned stimulus; b -- experiment; the respiration markedly increased in frequency and it is involved in a rhythmical [words are omitted at this point in the original text] of the unconditioned stimulus five seconds before it begins--

in the second second of the action of the conditioned stimulus; c -- experiment; conditioned reflex is manifested distinctly after 47 lapses in reinforcement (test for extinction); here, the frequency of respiration rapidly reaches 220 a minute, that is, the frequency of the unconditioned stimulus used in forming the given reflex, the cardiac activity is also involved gradually in the same rhythm.

The use of the inhibitory stimulus in the majority of cases also produced an involvement of respiration in the stimulus rhythm although it eliminated for a time the general conditioned excitation of the dog. The cardiac activity was involved in this rhythm also but comparatively rarely; however, in certain cases it was quite distinct (c).

The characteristics attested to the excessive and prolonged generalization of the conditioned reactions which occurred as well as to the great mobility of the vegetative reactions which were components of the given conditioned reflex. The diffuse nature of the stimulatory process in the progeny of chronically irradiated dogs was expressed also in inaccuracies and inadequacies of the conditioned reactions formed (raising of the contralateral extremity or both at the same time with drooping in the straps, extension of the extremity instead of the usual flexion, etc.).

Caffeine in a therapeutic dose of 0.003 grams/kilogram not uncommonly produced the development of phasic states. Most often, an ultraparadoxical phase was observed: a marked conditioned reaction to the inhibitor and a very weak reaction to the reinforcing stimulus. Side effects were observed also with reduction of the dose of caffeine by two-four-eight times. This indicated a weakness of the stimulatory process despite an adequately rapid formation of the conditioned reflex which required, obviously, a special explanation. This explanation may be given on the basis of results of testing the strength and mobility of the inhibitory process. These tests revealed a marked weakening of internal inhibition in all the experimental dogs which led to a notable loss of equilibrium of the nervous processes. In the offspring of the chronically irradiated dogs the lack of ability to extinguish elaborated reflexes in time was distinctly demonstrated. Usually no less than 50-60 lapses in reinforcement were necessary just so that the magnitude of the reflex being extinguished decrease more or less notably. After this, the reflex was maintained at low magnitudes for a very long time. The most constant here were the vegetative reactions which practically did not disappear, particularly the involvement of the respiration in

the thythm of the stimulus.

The attainment of "complete zero" proved to be exceptionally difficult even with the elaboration of differentiations. Even a comparatively coarse differentiation (tones of 200 and 500 cycles a second) was elaborated two or three times more slowly than in the control dogs. A distinction between the tones of 400 and 500 cycles per second was practically an insurmountable problem. A complete inhibitory effect in this case was observed only when the dog stopped reacting to both stimuli, that is, when repetition of the difficult problem led to a break in nervous activity.

Experiments with overstrain of the inhibitory process by means of a special prolongation of the time of the effect of the inhibitor to two or three minutes also showed an inadequacy of internal inhibition. Whereas dogs of the control group tolerated this test well, in the experimental dogs a distinct motor reaction occurred repeatedly during one or two minutes of the effect of the inhibitor, and then a loss of inhibition was observed in all the differentiations for two to three days. The injection of bromides in usual therapeutic doses (0.06 grams/kilogram), which was very frequently accompanied by the development of a phasic state (ultraparadoxical phase) also led to a disinhibition of differentiation. Bromide doses which were reduced by 10-15 times did produce these phenomena but did not give any visible improvement in conditioned reflex activity either. This indicated a modified reactivity of the experimental dogs.

Distinct results were obtained also from testing the mobility of the nerve processes by means of simultaneous reversal of a pair of stimuli. The offspring of irradiated dogs required three to four times more combinations and lapses in reinforcement than the control animals for this purpose. Here, in all cases the formation of an inhibitor proceeded considerably more slowly than the formation of a positive reflex and was not satisfactory even after 60-100 reinforcements.

The results of the examinations show that conditioned reflex activity of the offspring of chronically irradiated dogs is essentially altered. It is characterized principally by the characteristics which are inherent in dogs born of parents which were irradiated once (difficulty in extinction and revision of defense conditioned reflexes, reduced ability for fine differentiation, tendency toward breaks in nervous activity, facilitated development of paraboitoc states and the lack of ability to tolerate ordinary doses of bromides and caffeine). At the same time, the offspring of

chronically irradiated dogs were distinguished by particularly severe involvement of the inhibitory process, as a result of which the stimulatory process, even a weakened and altered one per se proved to be predominant by far. The ineffectiveness of internal inhibitions specifically may be explained by the rapid formation of positive conditioned reflexes, their inadequate degree of specificity, difficulty in extinction, facilitated irradiation of excitation in the cortex, prolongation of the stage of generalization and excess in the vegetative reactions which are components of the given motor reflex.

In evaluating the results of the investigations the facts should be emphasized primarily that internal irradiation of dogs, even that which does not produce the occurrence of radiation sickness in them brings about distinct changes in the condition of the cerebral cortex in the offspring of these animals. Here, the disturbance in the fine correlations of the body with altered environmental conditions is a sensitive index of the late consequences of irradiation, which cannot always be found by other methods. The regular disturbances in nervous activity detected show that the chronic irradiation in doses which do not produce diseases of the animal are far from being indifferent for their offspring. This may be seen from the distinct weakening in the strength and mobility of the nerve processes and a disturbance in their mutual equilibrium, which produces a definite biological inadequacy of the offspring of irradiated animals.

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Received 5 March 1959

Changes in Certain Electrocardiographic Indices in Acute Radiation Sickness Produced by Beta-Radiation and X-Irradiation

(An Experimental Investigation)

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From the Chair of Faculty Therapy (Head -- Professor A. A. Nechayev) of the Military Order of Lenin Academy imeni S. M. Kirov

Among the various clinical expressions of acute radiation sickness cardiovascular disturbances belong to a group of the essential and characteristic symptoms of this affliction. However, while the pathognomonic nature of the vascular changes in radiation afflictions is generally accepted (A. V. Lebedinskiy, T. S. Seletskaya, B. N. Mogil'nitskiy and M. S. Brumshteyn, S. S. Yal', G. A. Zedgenidze, D. S. Sarkisov and others), the effect of radiation factors on the functional condition of myocardium has not been made adequately clear to date. Along with statements of more or less pronounced changes in the cardiac muscle and in the electrocardiogram under the influence of radiation (P. D. Gorizontov, Yu. I. Arkusskiy, V. Fanardzhyan, K. Kyandaryan, Ye. Stefanov and others) the opinion is widespread in the literature according to which the myocardium is considered "not very vulnerable" under conditions of radiation injury, while the electrocardiographic changes, which are "only possible," are characteristic only of the severe injuries (M. N. Karlin and B. N. Mogil'nitskiy, I. A. Pigalev, N. A. Kurshakov and I. S. Glazunov, B. Gordon and others).

Nevertheless, observations of an experimental and clinical nature permit us to be convinced of the fact that the effect of radiation on the myocardium is indubitable and varied (F. D. Vasilenko, A. N. Bykhovskaya, I. N. V rkhovskaya and M. V. Arutyunova and others). Changes in the electrocardium have been noted as follows: disturbances in the rhythm, increase in the atrioventricular conduction, reduction in the voltage of the waves, increase in the systolic index (P. D. Gorizontov, Yu. I. Arkusskiy, V. Fanardzhyan, Ye. Stefanov), including also in clinical observations (A. A. Gus'kov, G. D. Baysogolov, L. Hempelman, Colin and others). These investigations and observations permit us to believe that electrocardiography in radiation injuries may be of importance for diagnosis and possibly an evaluation of the severity of radiation trauma, although to date under conditions of radiation injury it has been used rarely.

Experiments were performed on 48 rabbits, seven of which were controls and eight were exposed to X-irradiation; 24, to the effect of radioactive phosphorus (P^{32}); nine, to radioactive strontium (Sr^{89}). Before the irradiation and during the subsequent period a detailed clinical and hematological observation was made of the animals (dynamics of body weight, thermometry, observation of general condition and various systems, blood examination -- determination of hemoglobin, the red blood count and white blood count, the differential white blood count, sedimentation rate).

X-irradiation was given on an RUM-3 apparatus. It consisted of a single total-body irradiation with doses of 800-1000 r; the conditions of irradiation were the following: voltage 184 kv, current 15 ma, skin-to-tube distance 50 centimeters, filter 0.5 cm of Cu and one mm Al. Radioactive phosphorus and strontium were injected subcutaneously in the area of the anterior abdominal wall in a quantity of from one to three mC per kilogram of weight.

After the irradiation of the animals the clinical or hemotological expressions of radiation sickness were observed, which consisted in the pronounced cases of a disturbance in the general condition, a reduction in body weight, gastrointestinal disorders, blood changes, etc. Sickness in the animals in which a rapid and considerable loss of weight, a serious general condition accompanied by gastrointestinal disturbances, hemorrhagic manifestations, anemia, severe leukopenia (reduction in the leucocyte count to 1000 per cubic millimeter) were observed were considered third-degree injury. There were 14 such animals; they all died in the second-third week after radiation. The same clinical signs of radiation sickness but less pronounced than in the previous group were considered second-degree injuries. Specifically, the leukopenia in these cases varied within limits of from 2000 to 3000 per cubic millimeter (25-30 percent of the original leucocyte level). In all these animals (a total of 16) following a three-four week period of disease the condition became normal, and the blood composition became normal again. First-degree injury was established by the hemotological indices and by certain clinical data.

The electrocardiogram was taken for three-seven months. A record of it was made on the day after irradiation, and then every two or three days (during the acute period of the disease) and once every five to seven days in the subsequent months of the observation. The EKG recording was made with an EKP-4 apparatus in three standard leads. In reading the electrocardiograms the indices of the waves were reduced to standard millivolt data (1 mV = 10 mm).

The voltage of the P wave was altered in approximately half of the observations following irradiation. X-irradiation and irradiation with Sr^{89} produced a reduction in the atrial potentials, which not uncommonly was considerable (for example, X-irradiation, from 0.11 to 0.03 mV) and the irradiation with P^{32} was usually accompanied by an increase in the voltage of this index. Usually, the changes in the P wave were observed with third-degree injuries and at the climax of radiation sickness; however, in a number of cases they occurred as early as the day after irradiation and in cases of injuries of second- and even first-degree. The variations in the P wave voltage could not be explained by the tachycardia or bradycardia which developed after the irradiation.

The atrioventricular conduction time (P-Q) after the irradiation was changed in three cases two of which had been irradiated with X-rays and one, with Sr^{89}. In all these cases an increase was noted in the atrioventricular conduction time by 0.02 second, which was observed in third-degree injuries.

Disturbances in the intraventricular conduction time (QRS) were noted in five cases: in three, after X-irradiation; in one, after the effect of P^{32}, and in one, after the effect of Sr^{89}. In our cases (in two after X-irradiation and in two after the effect of isotopes) they were characterized by an increase in the duration of the QRS (second-third degree injuries, climax of radiation sickness); in one, by a reduction in the length of the QRS wave which was, apparently, associated with the developing tachycardia.

As is well known, the variations in the voltage of the QRS complex are characterized by a considerable dependence on the position of the heart in the chest cavity, in connection with which an analysis of the total index R + S has been recommended by a number of authors (O. V. Kachorovskaya, Yu. I. Arkusskiy). We have also studied the dynamic changes in this index. The following results were obtained.

After X-irradiation, in the great majority of observations as early as on the first day after the irradiation, a pronounced tendency was shown toward a reduction in the voltage of the QRS complex.

Thereby, second- and third-degree injuries were accompanied by more pronounced reduction in voltage than the mild injuries. On subsequent days of the observation (corresponding to the latent period) the voltage Δ + S increased somewhat (without, however, reaching the original level), and then dropped again at the climax of the sickness. In two cases (in one, second-degree injury; in the other,

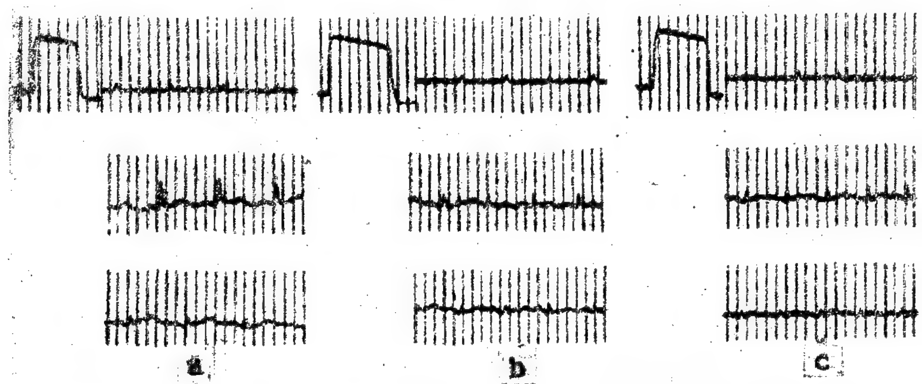
third-degree) the voltage of the ventricular complex on the second day after irradiation increased; however, in the case of a second-degree injury beginning with the fifth day after the irradiation it began to decrease, reaching 50 percent of the original level on the 19th day; in a case of third-degree injury a certain tendency toward an increase was found even later.

Variation in the R + S voltage after the effect of P^{32} showed different tendencies depending on the severity of the injury and the time which had elapsed since the irradiation. Thus, in mild injuries the voltage of the QRS complex increased somewhat during the course of the observation, particularly immediately after the irradiation. A similar tendency toward an increase in the QRS voltage (without signs of heart block) was noted also in the case of third-degree injuries. In the case of second-degree injuries the QRS complex decreased chiefly on the 37th-50th day after the irradiation, that is, after the elimination of the acute signs of radiation sickness. As a whole, the changes in the QRS after the irradiation with P^{32} were less pronounced than after X-irradiation.

The injection of Sr^{89} with all degrees of injury produced a regular reduction in the voltage of the QRS complex, which was different in its quantitative relationship. In mild cases it decreased only somewhat in the third week after the injection and came back to normal at the end of the fourth week; in second-degree injuries the reduction in the QRS voltage was noted immediately after the irradiation, whereby the greatest deviation came about on the 10th-11th day and was just as pronounced as after X-irradiation; in the case of third-degree injuries the voltage of the QRS complex decreased rapidly and considerably, remaining markedly reduced until the time of death of the animals. Examples of these changes in the QRS complex are presented in the Figure. Of the other characteristics of the QRS changes in the irradiated animals mention should be made of the occurrence of severe injury in certain cases produced by X-irradiation and Sr^{89} irradiation with electrical alteration on the QRS complex.

Clinical evaluation of the changes obtained in the initial part of the ventricular complex after radiation injuries, in our opinion, should be based on the fact which has been well established clinically and experimentally: there is a regular reduction in the voltage of the electrocardiogram in diffuse myocardial injuries of various origins (M. Ya. Ar'yev, P. Ye. Lukomskiy, L. I. Fogel'son and others). Therefore, the reduction in the voltage of the

QRS complex and in the P wave in the process of radiation injury should be regarded as a result of pronounced functional, and possibly, also anatomical (in the late period) changes in the myocardium produced by radiation. In this aspect the most considerable myocardial disturbances arise under the influence of X-radiation and β-radiation of Sr^{89}. The increase in the voltage of the QRS complex, including in the case of lethal injuries, which we and certain other authors have noted is evidence, apparently, of a lesser degree of involvement of the myocardium in a severe picture of the disease or is a reflection of distinct parabiotic disorders arising in the myocardium after irradiation.



Electrocardiogram. The Effect of Irradiation with Radioactive Sr^{89}. Third-Degree Injury:
a -- before irradiation; b -- after 13 days; c -- after 16 days; a considerable reduction is noted in the voltage of the QRS complex, particularly at the height of the injury.

The T wave in the control group did not show any regular variations in the voltage. After X-irradiation the voltage of it decreased chiefly in the severe and moderate injuries.

A reduction was observed on the sixth-seventh day (after irradiation) and was maintained throughout the entire period of the sickness. Sometimes the reduction in the T wave voltage was preceded by a certain increase in it, whereby it acquired a distinct peaked form. A tendency toward an increase in the T wave voltage was observed also after first-degree injuries. In three cases, after X-irradiation producing second- and third-degree injuries, the most considerable electrocardiographic changes were noted the day after irradiation: a marked reduction in the voltage of the QRS complex, a negative T wave in lead I or III with opposite shifts in the S-T interval in leads I and

III, that is, the picture of an acute focal injury occurred, particularly since the subsequent period was characterized either by the maintenance of a negative T wave or by the gradual transition of it to a small positive T wave, and the slow return of the S-T interval to the isoelectric line.

The effect of P^{32} and Sr^{89} in cases of first-degree injuries did not produce any essential changes in the T wave. In second- and third-degree injuries, as after X-irradiation, a regular tendency was observed toward a reduction in the T wave voltage, particularly after injuries produced by Sr^{89}, when the voltage dropped to 50 percent of the original value or more. In certain cases the reduction in T wave voltage was observed chiefly during the recovery period (30th-45th day after the irradiation, second-degree injury) and was maintained in the subsequent observation, which, apparently, attested to the occurrence of irreversible (morphological) changes in the myocardium as a result of radiation injury.

Therefore, in all types of irradiation with second- and third-degree injuries a regular reduction in the T wave voltage is observed, which is most pronounced after X-irradiation and Sr^{89} irradiation. Changes in the T wave were noted most often during the period of the climax of the sickness; however, in a number of cases they occurred even during the first few days after the irradiation.

In the control group more or less pronounced disturbances in the level or shape of the S-T interval were not found on dynamic observation.

After irradiation the changes in the S-T interval were noted in approximately one-third of the observations and occurred in all types of irradiation. Disturbances in the voltage of the S-T interval were of varied nature. Most often, this was a deviation from the isoelectric line by the S-T interval were of varied nature. Most often, this was a deviation from the isoelectric line by the S-T interval in one lead or in several leads simultaneously (concordantly); changes in the shape of the S-T interval were also observed (saddle-shaped, dome-shaped, etc.). Deviations and deformities of the S-T interval occurred chiefly at the height of the sickness; however, in six cases they were observed as early as on the second day after irradiation. The latter were cases of second- and third-degree injuries. As far as the relationship of the changes in the S-T interval to the injurious agent are concerned a relatively greater number of changes and a greater degree of expression of them came about in cases of Sr^{89} irradiation and X-irradiation.

Changes in the T wave and in the S-T interval are given importance in modern cardiology. Usually, they are regarded in connection with the nature of the metabolic processes in the ventricular myocardium (Ye. I. Borisova and V. S. Rusinov, A. F. Tur, L. I. Fogel'son and others), because they consist of a very dynamic electrocardiographic indices and react rapidly to various influences reflected on the metabolic processes in the cardiac muscle (M. Ya. Ar'yev, P. Ye. Lukomskiy, V. A. Shidlovskiy and E. A. Kyanvzhuntseva and others). The reduction in the T wave voltage in dynamic observations usually occurs with pronounced diffuse myocardial injuries (M. Ya. Ar'yev, P. Ye. Lukomskiy), deviation in the level of the S-T interval and a high T wave in the case of various disturbances of metabolism in the myocardium ("anoxia"), inversion of the T wave with the formation of a dome-shaped S-T interval and changes in the QRS complex with a subsequent picture of a gradual recovery are characteristic of the large-focus myocardial injuries (V. Ye. Nezlin, L. I. Fogel'son, V. G. Popov).

The data obtained indicate indubitable and essential disturbances in the myocardial function after irradiation.

Conclusions

1. Observations on electrocardiographic changes in acute radiation sickness produced by X-irradiation and the β-radiation of P^{32} and Sr^{89} permit us to believe that the radioactive isotopes, like X-irradiation, produce regular disturbances in the electrical activity of the myocardium.

2. Most frequently a reduction in the electrocardiographic voltage (R and T waves, QRS complex), a displacement or deformity of S-T interval are observed.

3. These disturbances may be noted in various phases of radiation sickness and sickness produced by P^{32} irradiation and not only in the case of severe injuries. Sr^{89} produces greater electrocardiographic changes than does P^{32}, and in a number of cases they are more pronounced than after X-irradiation.

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Received 7 August 1957

The Effect of Po^{210} on the Body

B. B. Moroz and N. P. Smirnova

The study of the biological effect of polonium as a source of α-radiation is of considerable interest for radiobiology. The current importance of this problem has increased particularly in recent years, when in connection with the development of the atomic industry the danger of the effect of polonium on people under industrial conditions has arisen (Anthoni, Davis, Couden, Jolley and others).

Po^{210} was discovered in 1898 by Marie and Pierre Curie; it is a practically pure α-emitter. The admixture of γ-radiation is usually not taken into account because of the little energy and low intensity of it: a total of seven to eight quanta of γ-rays with an energy of 0.773 MeV is emitted per million α-particles with an energy of 5.3 MeV. In undergoing α-disintegration, Po^{210} is converted to a stable isotope. The half-life period of Po^{210} is equal to 138.3 days. Thelength of the path of the α-particles of polonium in air under normal conditions is equal to 3.85 centimeters; in tissues it does not exceed 30-40 μ. Per millimeter of its path (in air) the α-particle of polonium forms 2510 pairs of ions, which characterizes its great ionization density; in tissues the ionization density is even greater -- it amounts to 2000-5000 ion pairs per μ of its route. Polonium may be obtained in an imponderable quantity of carrier. It is a heavy metal with amphoteric properties; in the chemical sense it may behave like its neighbors in the periodic table, bismuth or tellurium. In an alkaline, neutral or slightly acid medium it forms colloidal hydroxides. In the body it readily forms complexes with proteins, which determines the number of characteristics of its biological effect.

The first work on the study of the biological effect of polonium refers to 1913 (Fernau, Schramek, Zarzyski). In this work there are statements concerning the change in composition of the peripheral blood, the lengthening in the blood coagulation time, and the occurrence of hemorrhages in various organs affected by polonium in animals.

The local effect of polonium on the skin, mucous membranes, and wound regeneration has been studied by a group of roentgenocurie therapists (A. V. Bartel's, M. N. Pobedinskiy, E. G. Gracheva, Ye. N. Petrova, A. A. Fomina, N. Ivanov). With the direct effect of polonium on the human skin or on the animal skin (dose of from 0.7 to 513 ESE per hour) N. Ivanov found degenerative changes in the malpighian layer

of the epidermis and epithelium of the hair sheaths. The depth of injury exceeded the area of the path of α-particles in the tissues. In the experimental irradiation of skin wounds with α-particles of polonium it was possible to observe an acceleration or slowing of the peeling processes depending on the dose. Two days after the local application of polonium in a dose of 20-25 ESE for 24 hours deep-seated necrotic changes in the functional layer of the uterine mucosa were found; after smaller doses, degenerative changes in the functional layer with subsequent slowing of regeneration (A. V. Bartel's, Ye. G. Gracheva and others). With the application of plates covered with polonium in a quantity of 10 μC in a period of from 10 seconds to 30 minutes to the skin of mice as well as after immersion of such a plate through a skin incision in the epidermis signs of radiation injury were found -- the manifestation of anomalous nuclei, micronuclei, vacuolization, pycnosis, mitotic disorders (Kreyberg and Devik; Devik). When the plate is put under the skin the signs were expressed to an even greater degree; in addition, signs of general radiation injury were observed.

Polonium is a great hazard when it enters into the body through the respiratory tract, digestive tract, skin, and, in addition, experimentally by any parenteral route. According to the data of a number of Soviet authors, when polonium is injected under the skin in a quantity of 0.05-0.18 mC/kg an acute radiation sickness develops with death of dogs in a period of two-five weeks (V. S. Balabukha, I. K. Petrovich, V. P. Fedotov, S. M. Mikhaylovich and R. S. Krivchenkova). The absolutely lethal dose for dogs is 0.02-0.03 mC/kg; this quantity causes a subacute radiation sickness (V. S. Balabukha, Z. I. Poluboyarinova, B. I. Lebedev). After the injection of 0.2 mC/kg of polonium by mouth death of 100 percent of the animals occurs in late periods, after 7-12 months, with a chronic course of the process (A. Ya. Shulyatikova, V. S. Balabukha). Rabbits and rats apparently are somewhat less sensitivie to polonium. Acute injury after the parenteral injection of the same preparation of polonium develops after the injection of 0.1-0.2 mC/kg (V. V. Vasil'yevskaya, B. B. Moroz, N. P. Smirnova, M. S. Uspenskaya, A. Ya. Shulyatikova, A. G. Izergina, T. L. Zayets, M. G. Zotova and others). Chronic injury, which also causes 100 percent mortality of the animals, can be produced in rats by the subcutaneous injection of 0.01 mC/kg of polonium (M. G. Zotova) or by the oral administration of one mC/kg (N. P. Smirnova). In rabbits subacute injury with 100 percent mortality of the animals after two-five months was obtained

after the subcutaneous injection of 0.03 mC/kg of polonium (B. B. Moroz and V. V. Vasil'yevskaya).

In the literature there are actually no data concerning the quantities of polonium which can be tolerated by animals after injection of the preparation into the body. At the Geneva Conference on the Use of Atomic Energy for Peaceful Purposes in 1955 data were presented to the effect that the minimum effective dose for rats after intravenous injection is 0.75 and 0.5 μC/kg (Anthoni, Davis, Couden, Jolley). Under these conditions, the toxic effect was expressed only in a transitory mild form of kidney injury, accelerated aging and a considerable reduction in the life span. The dose of polonium representing the boundary between the minimally effective dose and the tolerance dose is 0.25 μC/kg. On the basis of calculated data the authors arrive at the conclusion that the maximum permissible dose for man is 0.003 μC/kg of polonium.

In the investigations of foreign authors the determination of the toxicity of polonium according to the minimum lethal dose -- the LD_{50} is accepted. Fink and others in experiments on rats established an $LD_{50/20}$ of 15 μC/kg after intravenous injection; an $LD_{50/30}$, of 30 μC/kg. Finkel and his co-authors confirmed these data, establishing the fact that the $LD_{50/30}$ for mice is within the limits of 30-40 μC/kg after the intravenous injection of polonium in the same solvent. According to Hursch, after the intravenous injection of polonium into rats in a dose of 36 μC/kg the average life span was equal to 22 days.

Data concerning the comparative toxicity of three α-radioactive elements -- radium, plutonium and polonium -- obtained experimentally and by calculation (Fink) are of definite interest. The most toxic of these elements was polonium, whereby this was particularly distinctly expressed in the acute forms of injury. Among the possible causes accounting for this marked difference in toxicity the authors consider the half-life period, the degree of retention in the body as a result of unequal excretion, the quantity of energy liberated with α-disintegration, as well as the characteristics of the distribution of the elements in the body. The authors consider the latter the decisive cause of the differences in the toxicity of the three elements. According to the $LD_{50/30}$, expressed in physical roentgenequivalents and by taking into consideration the half-life period, the energy of α-particles, the energy of disintegration of the daughter products of radium, and the differences in excretion of the elements the toxicity of polonium was 120 times greater than the toxicity of radium.

The excretion of polonium after entering the body by any route is accomplished chiefly by the gastrointestinal tract and by the kidneys. In the excretion of polonium from the body all the digestive glands participate. Polonium is found in the saliva, bile, gastric juice, small intestinal juice, (S. R. Perepelkin). The excretion of it occurs also through the skin glands (B. N. Tarusov). In his time Lacassagne found that polonium is excreted chiefly through the kidneys after parenteral administration (1924-1928). According to recent data, the excretion in the stool exceeds the polonium excretion in the urine by many times. Excretion of polonium in the stool after the intravenous injection of it into rats (10-30 μC/kg) is maximal on the third day and exceeds its excretion in the urine by 60 times. Afterwards, the 24-hour excretion of polonium in the stool is reduced (Fink). According to the data of M. A. Zaytseva, following a subcutaneous injection of 0.075-0.1 μC/kg of polonium into rats 124 times more of it is excreted in the stool on the fifth day than in the urine. After inhalation (observations on people -- Foreman, Mass, Eustler) the excretion of polonium in the stool during the early period exceeds its excretion in the urine by two or three orders of magnitude; after five months the difference becomes ten-fold.

Polonium excretion begins from the first few minutes after the polonium enters the body. Thus, after the subcutaneous injection of polonium it was found in the first portion of urine in dogs with exteriorized ureters (Z. I. Poluboyarinova). The excretion of polonium proceeds most intensely during the first few days, which leads to a rapid and noticeable reduction in its content in the body compared with the dose administered. At later periods the excretion of polonium is maintained at a low and quite constant level. After the administration of polonium by mouth, from 30 to 40 percent of the dose is excreted in the stool during the first few days, which is evidence of a low degree of polonium absorption from the gastrointestinal tract (V. S. Balabukha, 1954). According to Fink, less than 10 percent of the quantity administered is absorbed through the gastrointestinal tract. After the intravenous injection fo 10-30 μC/kg into rats the intensity of excretion of polonium drops from five percent of its quantity in the body on the third day after the injection to 1.3 percent of the residual polonium by the 80th day, and it remains at this level up to the 300th day. As a result of excretion and loss through radioactive disintegration 70 percent of the quantity of polonium administered remains in the body on the 10th day; on the

30th day, 50 percent; 300 days after the injection, a total of one percent of the dose administered (Fink). Similar data have been obtained in similar experiments on mice (Finkel and others). Therefore, 30 days is considered the biological half-life period of polonium (loss of the administered dose of 50 percent through excretion and radioactive disintegration). Anthoni and coauthors determined the period of biological half-life of polonium to be 35 days after intravenous injection.

A diffuse type of distribution in the body with a preferential deposition in the organs of the reticulo-endothelial system is characteristic of polonium. Several minutes after subcutaneous injection it appears in the blood; its concentration increases up to the second or third day, and then a slow reduction of it is observed (L. L. Khamayde). After intravenous injection the reduction in polonium concentration in the blood begins after 10 minutes (Gallimore and others). Simultaneously, polonium may be found autoradiographically or by a radiochemical method in practically all the organs and tissues (Lacassagne and co-workers, Ye. V. Erleksova, Fink, Finkel and others, Gallimore and others, L. L. Khamayde and others). However, polonium is accumulated in a larger quantity in the lymph nodes, spleen, liver, as well as in the cortical layer of the kidneys, thymus, sex glands. A relatively high degree of accumulation of polonium has been shown in the lactating breast (Lacassagne and Cotelle), a deposition of it in an inflammatory focus (L. L. Khamayde, A. I. Chuchukalo), and in tumor tissue, particularly that undergoing disintegration (Vekerdi and others).

The quantity of the element and the route of administration in the body have essentially no effect on the nature of polonium distribution. Inhalation constitutes an exception; hereby, up to 30 percent of the dose is retained in the lungs; the rest enters the blood and is subject to excretion and distribution just as after the intravenous route of administration (Fink). However, the opinion exists that the distribution of polonium after oral administration differs somewhat from that after intravenous administration, which, incidentally, does not lead to any differences in the toxicity of the radioactive substance (Stannard, Della Rosa, Thomas). Distribution and excretion of polonium after inhalation reflects the entrance of the element into the body through the respiratory and digestive tracts (Berke, Di Pasqua). Depending on the time which has elapsed after injection, a certain redistribution of polonium occurs. Twenty-four hours after intravenous injection of 10-30 $\mu C/kg$

of polonium into rats the highest specific concentration of the element (Fink) was noted in the mesenteric lymph nodes (10.4 percent per gram of weight of the organ); then in the spleen (5.1 percent), kidneys (3.6 percent), blood cells (2.3 percent), liver (1.69 percent). Ten days after the injection the greatest quantity of the polonium is found in the spleen, which contains 9.3 percent; then, in the mesenteric lymph node (6.1 percent), kidneys (4.3 percent), blood cells (1.24 percent), liver (1.34 percent). The content of polonium in the brain is insignificant for the entire period following the administration and usually does not exceed 0.05 percent. These data are in agreement with the investigations of Ye. V. Erleksova, L. L. Khamayde and other authors.

On histoautographic investigation γ-particle tracks are found coming from the reticulo-endothelial cells, parenchymatous organs, epithelium, and from the external structural elements (Ye. V. Erleksova). The characteristics of polonium distribution, like that of other radioactive elements, are associated with its physico-chemical properties. Polonium enters the blood in a highly dispersed state and it is distributed diffusely throughout all the organs. In a neutral medium of the body it shows its property of forming colloidal complexes with proteins. The colloidal particles formed are sorbed onto the erythrocyte membranes, and are phagocytized along with them by the istiocytes and macrophages (B. N. Tarusov, Ye. V. Erleksova, L. L. Khamayde). Therefore, in the late periods following injection of polonium it accumulates chiefly in the reticulo-endothelial cells in the form of large particles. These large particles are found on the autoradiographs in the form of "stars," do not penetrate through membranes of excretory organs and, for practical purposes, remain in the body, creating foci with a very great radiation energy density (B. N. Tarusov, L. L. Khamayde, Ye. V. Erleksova, Gallimore and others). The dose rate of irradiation in the center of a macrophage, according to the data of B. N. Tarusov, amounts to 30-40 r/day; in the vicinity of it, 5 to 10 r/day. The greater toxicity of polonium in comparison with other α-active elements is explained by the tendency of it toward aggregation and consequently the creation of local powerful foci of irradiation in organs with a high degree of radiosensitivity (B. N. Tarusov, Fink).

The calculation of <u>tissue doses</u> of irradiation made with the arbitrary assumption of a uniform distribution within the organ shows that after the intravenous injection of 25 μC/kg of polonium into mice the spleen and lymph nodes

receive, respectively, 170 and 48 rep/day during the initial period; after 120 days, 7 and 1.7 rep/day (Finkel and others). In chronic polonium injury produced by the implantation of 78.5 mC/kg of the preparation in a gelatin capsule under the skin, the total dose of radiation received by the renal cortex and spleen over the course of approximately 200 days amounts to approximately 10,000 rep (Kreyberg, Devik).

Gallimore, Boyd and Stannard assume the possibility of formation of polonium aggregates in injectible solutions; therefore, the solvent used is of definite importance for the toxicity and distribution of polonium. In the works of American authors polonium chloride is usually used. Soviet authors have injected polonium in a nitric acid solution neutralized with alkali with the addition of mannitol. The latter forms a readily soluble complex compound with polonium. Gallimore also points to the possibility of disintegration of polonium aggregates in organs, the washing out of it into the blood, and the excretion of it through the natural excretory systems.

Observations on people who were injected intravenously for therapeutic purposes with 0.17-0.3 μC/kg of polonium made it possible to obtain data on the excretion and polonium concentration in the blood similar to results obtained experimentally on animals (Fink).

As has been noted above, the nature of radiation sickness depends on the quantity of polonium and the method of administration of it. The development of the pathological process is conditioned essentially by the individual sensitivity or resistance of the animals (I. A. Pigalev, 1954).

The clinical picture of polonium injury in different species of animals is basically unitypical. In connection with this, we should like to limit ourselves to a brief description of the clinical picture of the acute and subacute forms of radiation sickness in dogs (V. P. Fedotov).

During the first few days after the injection of radioactive substance the animals are apparently no different from normal. The latent period lasts usually five to seven days and is shortened somewhat only after the administration of large quantities of polonium. Afterwards, the animals become sluggish; there is a loss of appetite, the body weight decreases, and there is a leukopenia. All these signs continue to progress, diarrhea is frequently noted with mucus or an admixture of blood, and there is vomiting and a marked thirst. Photophobia, conjunctivitis, rhinitis develop, and punctate hemorrhages are found on the oral mucosa and conjunctiva of the eyes. In cases of subcutaneous administration of polonium edema and hyperemia is noted at the site of in-

jection; then, there is an infiltrate which is replaced by necrosis and the occurrence of an ulcer with undermined, slowly granulating edges. Before death the experimental dogs lie motionless, do not react to stimulation, refuse food; the leucocyte count goes down to 500 per cubic millimeter; the weight drops to 30-40 percent of the original. The loss of appetite, occurrence of vomiting, diarrhea and weight loss attest to serious disturbances in the function of the gastro-intestinal tract. In experiments on dogs under conditions of acute and subacute injury considerable changes are found in the secretory activity of the gastric and small intestinal glands, which is manifested in hypersecretion (S. R. Perepelkin).

In a subactue course the signs of radiation sickness have a lesser degree of expression primarily. However, the presence of a "critical period" is very characteristic. The fully developed picture of radiation sickness was usually demonstrated after two or three weeks. If the animals did not die their condition subsequently improved. The period of relative compensation lasted one and a half to two weeks. Usually, the condition of the animals suddenly deteriorated markedly, and after several days they died. An increase in body temperature was noted in part of the animals (25-40 percent) at the climax of radiation sickness.

As a rule, the increase in temperature on the basis of the data of the pathological examination could be tied in with the development of infectious complications. At the same time, cases occurred where at autopsy the presence of, for example, pneumonia was determined, whereas no increase in body temperature had been noted in the animal. These observations can attest to one of the characteristics of the courseof the infectious process in radiation sickness (B. B. Moroz).

In the late periods in cases of the subacute course of the radiation process indolent ulcers occurred in the animals not only at the site of injection of polonium but also in other areas of the body. In dogs, for example, they were most often localized in the lumbar area or on the feet -- symmetrically on the posterior or on both anterior and posterior extremities (V. P. Fedotov).

The clinical picture of chronic radiation sickness has practically not been studied. Scattered observations constitute evidence of the phasic course of the process: disorders of functional activity of various systems are replaced by periods of relative compensation; a marked exhaustion of the animals and increasing changes in the kidneys are also characteristic.

Study of the picture of the peripheral blood (I. K. Petrovich) has shown that in acute injury by polonium a lymphocytopenia and neutropenia are observed, and before death of the dogs an aleukia occurs. The red blood count also decreases, reaching 50 percent of the original quantity at the time of death. The color index increases, and becomes higher than unity. A subacute course of the injury is characterized by a slow but progressive decrease in the leucocyte, reticulocyte and erythrocyte counts and in the hemoglobin. With the superimposition of infectious complications leucocytosis was observed; a distinctive feature of it was the absence of any increase in young forms of cells (A. G. Izergina and V. V. Snegireva).

With a chronic course of the disease with death after five-seven-nine months the lymphocyte count was reduced at all the times observation was made; the total leucocyte count was at the lower limits of normal. Before death a neutrophilia and monocytosis were noted. Anemia which developed from polonium injuries was apparently not connected with a disturbance in hemoglobin synthesis (Thomas, Altman, Stannard, Salomon). These authors, utilizing the uptake of carbon-tagged glycine as an index, showed that the relative rate of hemin and globin synthesis are not noticeably changed.

Essential disturbances were found in the <u>blood coagulating system</u> as well as changes in the <u>capillary fragility and permeability</u> (A. S. Petrova, I. K. Petrovich, S. M. Mikhaylovich and R. S. Krivchenkova). The platelet count in the blood after acute polonium injury decreases sharply. The coagulation time of the blood increases by one and one-half to three times beginning with the first day of the sickness; death of the dogs occurs in the presence of a marked disturbance in the process of blood coagulation (S. M. Mikhaylovich and R. S. Krivchenkova). Distinct and persistent disturbances were noted in the capillary fragility (experiments with cupping tests) and an increase in permeability. The clinical expressions of the disturbance in the processes of blood coagulability, fragility and permeability of the vessel wall in the form of hemorrhages from the nose, gums, rectum appeared later (S. M. Mikhaylovich and R. S. Krivchenkova). With a chronic course of the injury the changes in the blood coagulating system developed in particularly marked form before death of the animals (A. S. Petrova). A disturbance in the activity of the <u>cardiovascular system</u> was studied in the <u>chronic experiment on rabbits with acute</u> polonium injury (0.1 mC/kg subcutaneously).

In the early periods of the injury considerable variations were noted in the blood pressure. At the climax of

the sickness hypotension developed which progressed; before death of the animals the blood pressure dropped to 40-50 percent of the original level. Pronounced electrocardiographic changes were also observed at the climax of radiation sickness and constituted evidence of dystrophic changes in the myocardium. Respiration gradually slowed up, beginning with the first few days of the sickness (B. B. Moroz, S. P. Grozdov).

Study of the pathological picture in acute polonium injuries did not permit the detection of any essential characteristics by comparison with acute radiation sickness caused by external ionizing radiation (N. A. Krayevskiy, E. V. Erleksova, G. A. Tagunova, A. Ye. Ivanov, Fink). Nevertheless, very early changes in the blood vessels may be noted, particularly in the capillaries which were expressed in cloudy swelling of the endothelium, separation of the fibers and plasmatic impregnation of the blood vessel walls. A greater congestion of the internal organs was characteristic. In the acute and chronic forms changes were also noted which were characteristic of radiation injuries; however, kidney changes were typical. The kidneys were reduced in size chiefly because of a marked thinning out of the cortical layer; they became dense; progressive atrophic changes were noted in the tubules and glomeruli; collagenization of the stroma; the picture of a distinct nephrocirrhosis [granular kidney] developed; in the kidneys considerable quantities of polonium were found, chiefly in the epithelium of the convoluted tubules. On microscopic examination the greatest changes were shown also in the epithelium of the convoluted tubules.

A small number of investigations has been devoted to a study of the condition of the metabolic processes. The main ideas have been obtained only with respect to a disturbance in protein and carbohydrate metabolism. In animals with acute polonium injury an increase was found in the excretion of total nitrogen and urea nitrogen in the urine (K. I. Zykova, Z. I. Poluboyarinova) as well as an increase in the concentration of the nonprotein nitrogen in the blood (V. S. Balabukha, T. L. Zayets). When there is a marked reduction in food consumption the nitrogen excretion in the urine is reduced. The total quantity of protein in the blood of dogs and rabbits is unchanged when the process has an acute course (V. S. Balabukha, T. L. Zayets). At the same time, essential changes have been found in the fractional composition of the plasma proteins (or serum proteins).

In dogs and rabbits a reduction has been noted in the

concentration of albumin and an increase in the concentration of the α-, β- and γ-globulins. During the course of the sickness the changes found increase. The albumin-globulin ratio is altered correspondingly. In the plasma of rabbits a marked increase is also noted in the concentration of fibrinogen, beginning with the first day of the sickness; at the same time, an increase is noted in the uptake of tagged amino acid (radiomethionine) in the plasma proteins -- fibrinogen and pseudoglobulins (T. L. Zayets). A marked reduction was found in the concentration of desoxyribonucleic acid in the liver of rats injured by polonium. A disturbance in the structural viscosity of the liver DNA and a reduction of the nitrogen from purine and pyrimidine bases. In the DNA preparations isolated from the liver at various periods of radiation sickness by the radioautographic method the presence of polonium was found (M. S. Uspenskaya).

The concentration of the SH-groups was notably reduced in the proteins of the liver and spleen of rats intoxicated with polonium. In the proteins of the kidneys and muscles a reduction in the quantity of SH-groups was expressed to a lesser degree; in the brain proteins it was unchanged (M. G. Zotova). In the investigations of the cholinesterase activity under conditions of acute injury Ye. N. Petrovnina found an increase in the activity of the enzyme in the liver, spleen, lungs during the early period of the sickness and an inhibition of it, which developed in the later period of the disease. In the brain the cholinesterase activity did not show any tendency toward inhibition.

In experiments on dogs (V. P. Fedotov) and on rats (A. Ya. Shulyatikova) in acute polonium injury a marked reduction in the glycogen content in the liver and muscles was found. Before death almost a complete exhaustion of the glycogen content in the liver and muscles was found. Before death almost a complete exhaustion of the glycogen reserves in the liver and muscles was found; the blood sugar curves during a glucose tolerance test assumed the form of diabetic curves. An instability of the glycogen and lactic acid concentration in the blood were noted (A. Ya. Shulyatikova). In experiments on angiostomized dogs considerable disturbances were found in the sugar-fixing function of the liver under conditions of a glucose tolerance test (V. P. Fedotov) at approximately the same time at which, according to the data of A. Ya. Shulyatikova, a marked reduction occurred in the concentration of glycogen in the liver and other organs. In experiments on angiostomized dogs a parallel study was made of the barrier function of the liver by means of radioactive colloidal gold. A notable reduction

on the barrier function of the liver was observed during the last few days of acute radiation sickness (V. P. Fedotov).

A high degree of sensitivity of the liver to the effect of polonium was found in chronic radiation sickness in rats produced by the repeated injection of 2 μC/kg of the radioactive substance. An acute liver injury was noted, expressed in cirrhotic and necrotic changes, extensive proliferation of the bile ducts and others (Anthoni and coauthors).

In the literature there is no information concerning the disturbance in lipoid metabolism in polonium injury. The condition of the mineral metabolism has not been clarified either. There are only certain general data concerning the state of iron metabolism (N. P. Smirnova). With a chronic course of radiation sickness no essential changes occur in the concentration of the total iron in the body of rats. An apparent increase in the iron concentration per gram of weight occurs in the spleen, evidently because of the atrophy of the lymphoid elements. The entrance of exogenous radioactive iron (Fe^{59}) into the spleen, liver and erythrocytes is also reduced, which is apparently associated with a disturbance in the function of the reticulo-endothelial system (disturbance in hematopoiesis has not been noted under these experimental conditions). On the other hand, there are data in existence to the effect that the function of the reticulo-endothelial elements of the liver and spleen is essentially unchanged (Tuttle, Baxter).

In experiments performed on rats with acute radiation sickness periodic phasic changes in the respiratory gas exchange have been found (N. P. Smirnova). Phases of a marked gas exchange have been found (N. P. Smirnova). Phases of a marked gas exchange disturbance ($\pm$ 40-70 percent) alternate with periods of recovery, when the metabolic level corresponds to the original level.

One of the most vulnerable organs after the effect of polonium is the kidney which is partly associated with polonium excretion. The part played by the kidneys as "critical" organ stands out most prominently in chronic injury. The maximum polonium concentration in the kidneys after a single administration (within the range of 0.25-35 μC/kg) exceeds the average polonium concentration in the entire body at the time of administration by ten times for many days. Similar data have been obtained also with respect to the spleen (Anthoni and others; Kreyberg and Devik). However, no signs of regeneration were noted in the kidneys, whereas in the spleen at certain periods regenerative pro-

cesses were observed. These data made it possible to criticize the established concepts of radiosensitivity of the tissues (Kreyberg, Devik). On the other hand, Stannard doubted the principle of selection of a critical organ in injury by isotopes of the polonium type. According to his data, the relatively greater polonium concentration in the kidneys and spleen when the element is administered fractionally is not reflected in the data of histopathological investigations.

A study of the kidney function in the experiments on dogs with exteriorized ureters in acute injury showed a considerable reduction in diuresis after water and salt excesses. The chloride concentration in the urine also decreased; at the climax of radiation sickness albumin appeared in the urine. The specific gravity of the urine at the beginning of the sickness increased; afterwards, it gradually decreased and became stable during the final period of the animals' lives. A reduction was found in the effective renal blood flow and a marked reduction in the secretory activity of the tubules (Z. I. Poluboyarinova). The author believes that changes in the functional activity of the kidneys are produced first by a reduction in the renal blood flow of the tubular segment of the nephron and a disturbance in the resorptive and secretory functions of the tubules and then also of glomerular filtration.

In acute polonium injury considerable changes occur in the central nervous system. Disturbances in the functional activity of the nervous system are expressed very demonstratively in the clinical picture. Signs of a certain excitation can be found directly after the administration of the radioactive substance. A depressive condition and an indifference to the surroundings are observed in animals at the climax of radiation sickness, particularly before death. Changes have been described in the functions of the auditory and visual analyzers in dogs (I. A. Pigalev). Ulcers on the skin and mucus membranes, epilation, etc., undoubtedly can be attributed to neurotrophic disturbances.

Study of the functional condition of the central nervous system of animals in acute injury showed a marked increase in the electrical waves, an increase in reactivity and excitability of the visual analyzer in response to light stimulation 30-50 minutes after the administration of polonium (0.2 mC/kg subcutaneously). At the same time, the conditioned-reflex activity is essentially unchanged (Z. A. Yanson). In experiments on white rats it has been established that as early as 15-20 minutes after the administration of 0.1 mC/kg of polonium subcutaneously a weakening of the basic cortical processes -- excitation and inhibition

-- occurs with a relative preservation of the complex unconditioned reflexes (A. G. Izergina).

Beginning with the second or third day after the administration of polonium an instability was observed in the functional condition of the central nervous system. The electrical activity of the cerebral cortex, reactivity and excitability of the visual analyzer at times would increase and at times would decrease; the magnitude of the motor reaction was inconstant. The conditioned reflexes became unstable, sometimes were omitted, and inhibition of the unconditioned food reflex was noted. Afterwards, signs of profound cortical inhibition and inhibition of the subcortical structures increased. The electrical activity lessened, the excitability and reactivity in response to external stimuli became weaker, and the conditioned reflexes disappeared. Against this background periods were found in the rats of more or less complete recovery of cortical activity. By means of functional tests (injection of caffeine, adrenalin, sodium bromide) disturbances were found also in the central nervous system during these periods.

In acute polonium injury the metabolic processes of the nerve tissue mediators are altered. A disturbance in the synthesis and rate of destruction of acetylcholine was shown in the brains of white rats by Ye. N. Petrovnina. The cholinesterase and cholinacetylase activity changed in parallel during the initial period of the sickness (phase of increase followed by reduced activity). Subsequently, in the presence of a reduced cholinacetylase activity the cholinesterase activity was increased, or the reverse relationships were observed. A reduction in the acetylcholine concentration in the brain occurred in the early periods of the sickness. Afterwards, a tendency was noted toward an increase in the acetylcholine concentration.

Morphological changes in central and peripheral nervous systems were studied in dogs in subacute polonium injury after quantities of 0.02-0.05 mC/kg (N. A. Krayevskiy, V. V. Portugalov, K. U. Morozova, B. I. Lebedev). Changes in the nerve cells were found in all centers of the brain (chromatolysis or intensely stained cells); however, the nuclei of the hypoglossal and vagus nerves, the thalamus, basal ganglia and cerebral cortex are areas which are most injured. In the neurons of the intervertebral ganglia and particularly the sympathetic ganglia widespread changes are found in the form of chromatolysis. By the histoautoradiographic method the presence of polonium was found in these ganglia. A high degree of sensitivity of the embryonic nerve tissue to α-radiation of polonium was established in experiments with

the study of the mitotic activity of the neuroblasts of grasshopper embryos (Rogers). A suppression of mitotic activity was found to be greatest for the effect of polonium, followed by X-rays and β-radiation under the same experimental condition.

In acute and subacute radiation sickness caused by polonium the resistance of the body to infection is reduced (I. A. Pigalev). In mice injured by polonium which were then injected with a pathogenic pneumococcus, pneumococcal sepsis developed more quickly. In the organs of irradiated mice a larger number of microbes were found than in control mice (B. B. Moroz). After the combined effect of polonium (0.1 mC/kg subcutaneously) and tetanus toxin certain characteristics of the course of radiation sickness and tetanus intoxication were found (B. B. Moroz). The injection of tetanus toxin in non-lethal doses into rats at various periods of the tetanus culture in addition to the administration of polonium led to an increase in the pathological process in the majority of experiments and to the earlier death of the animals. At the same time, local signs of tetanus were usually less pronounced. With the simultaneous injection of polonium and tetanus toxin in a lethal dose an inhibition of the development of the signs of tetanus was usually observed along with an aggravation of the radiation process. Under conditions of such a combined effect the rats died earlier than animals affected by polonium alone and later than normal rats which had been given tetanus toxin. Signs of general tetanus developed later and not in all the animals.

Changes in acquired immunity in animals injured by polonium have been studied in experiments with immunization with tetanus and diphtheria toxoid and typhoid vaccine (I. A. Pigalev, B. B. Moroz, V. V. Vasil'yevskaya). It has been established that the injection of polonium into animals which have a strongly developed immunity does not lead to any essential changes in the titer of the irradiated animals compared with the controls.

A disturbance in the process of immunogenesis was shown distinctly in experiments with immunization and particularly reimmunization of animals injured by polonium. Reimmunization at the climax of radiation sickness led only to a slight increase in the antibody titer the level of which was several times lower than in the control rabbits. A disturbance was also found in the phagocytic function of the reticulo-endothelial system. A marked reduction in the uptake of dye (trypan blue) by the liver reticulo-endothelial cells was observed at the climax of radiation sickness

(A. I. Chuchukalo).

The immjnological reactivity of tissues of animals injured by polonium is also unchanged (V. V. Vasil'yevskaya). The areactivity of an isolated loop of small intestine existing in immuned guinea pigs with respect to diphtheria toxin is replaced by a pronounced reaction to the toxin. It was found that immunization with tetanus and diphtheria toxoids and with tetravaccine both before and directly after the administration of polonium exerts a favorable effect on the course of radiation sickness. In the immune animals a slower decrease in weight was observed; the leukopenia was manifested only slightly; and the animals died at later periods of time than the non-immune animals (V. V. Vasil'yevskaya, N. N. Klemparskaya, O. R. Nemirovich-Danchenko and others).

Therefore, in an organism affected by polonium disturbances are noted of the important mechanisms of natural immunity, of the processes of immunogenesis; the sensitivity of cells to microbial toxins is altered; characteristics are observed in the course of infectious processes, etc. At the present time, there is no basis for speaking of any kind of characteristic features in the changes of immunity in radiation sickness caused by polonium. Mention should be made of this, because it is well known that polonium accumulates chiefly in the reticulo-endothelial system, and direct injury of the latter may be very considerable.

In connection with what has been stated it is obvious that reactivity in animals affected by polonium should be altered. However, this problem has been very little studied. The significance of the original condition of the body and primarily of the condition of the center and vegetative nervous systems have practically not been investigated. We can note only that the administration of polonium into rabbits (0.07 mC/kg subcutaneously) at the height of anesthetic sleep leads to development of a more serious disease picture (B. B. Moroz).

Changes in the reactivity of the irradiated organism and in its various systems are shown through the use of a method of functional stresses. Study of the reactivity of the cardiovascular system to certain pharmacological agents has made it possible to show changes in the conduction and excitability of the myocardium (according to electrocardiographic data) and in the blood pressure reaction, in the development of which two periods may be distinguished (B. B. Moroz and S. P. Grozdov). The first period began immediately after the administration of polonium, ended at the climax of radiation sickness, and was characterized by an

increased sensitivity of the heart to adrenalin and doryl, considerable variations in the magnitude of the pressor affect of adrenalin. In the second period a reduction is observed in the sensitivity of the heart to pharmacological agents, a regular reduction in the magnitude of the pressor affect of adrenalin, a decrease and inversion of the depressor reaction to nitroglycerin. While the disturbances in the first period are apparently associated with signs of instability of the vegetative innervation, in the late period injury of the cardiac muscle probably occurs along with a decrease in the extracardiac reflexes. In rats injured by polonium a weakening or inversion of the reaction of the ear blood vessels to acetylcholine is found (V. V. Vasil'yevskaya).

An increase in the sensitivity to adrenalin on the part of rats injured by polonium has been noted by A. G. Izergina on the basis of a study of higher nervous activity. The administration of adrenalin in a dose of 0.001 milligrams per kilogram did not cause any changes in the magnitude of the positive conditioned reflexes in healthy rats. In animals injured by polonium an inhibition of conditioned reflexes was observed thereby. A more intense excretion of sugar by the liver as a response to the administration of adrenalin was shown by V. P. Fedotov. Under these experimental conditions study of the sugar curves following the administration of insulin made it possible to establish the presence of a more pronounced and more prolonged phase of hyperglycemia at the climax of radiation sickness, in connection with which the hypoglycemic state occurred later than in healthy dogs. Sensitivity of irradiated animals proved to be increased also to caffeine and sodium bromide (A. G. Izergina).

Study of the reactivity of polonium-injured rabbits to pyrogenal showed changes in the functional condition of the heat-regulating centers in the course of radiation sickness (B. B. Moroz). During the first few hours after the administration of polonium a higher temperature reaction was noted in the majority of animals than normal. Afterwards, an instability of this reaction was observed. In the final period of radiation sickness a considerable weakening of the temperature reaction was noted; in individual animals pardoxical reactions occurred; a reduction of temperature in response to the injection of pyrogenal. It was also noted that the gas exchange reaction to a cold stress in animals injured by polonium (0.1 mC/kg subcutaneously) is inconstant and may vary from zero to excessive (N. P. Smirnova). The tissue reactivity is also changed. Changes have been

described in the contractile power of the small intestine of white mice and guinea pigs in response to histamine and acethycholine (Z. I. Poluboyarinova).

In summarizing the data presented it should be noted that many aspects of the biological effect of polonium remain inadequately studied. Among them, first of all, is the problem of the tolerance doses of polonium as well as the effect of small doses (chronic radiation sickness, late consequences). Experimental acute polonium injury has been relatively well studied.

It should be noted that no essential characteristic features of acute polonium injury have been made out by comparison with acute radiation sickness following external irradiation. The low degree of expression of the early reaction to the injection of polonium is brought about by the lesser intensity of the radiation effect. The nature of distribution of the radioactive substance, retention of it in the body for a long time, the continuous nature of the internal irradiation, and the ionization density can apparently be more distinctly expressed in the chronic course of radiation sickness caused by polonium. Despite certain characteristics in the ionization process and in the excitation of molecules after α-radiation, the primary physico-chemical processes are probably the same after the effect of different types of ionizing radiation. In this connection we may refer to the data of B. N. Tarusov and L. L. Khamayde who showed the presence of hemolytically active substances in the tissue of animals which occur as the result of chain oxidation reactions in lipids both after external and internal irradiation.

Phasic disturbances in the functional activity of various systems as well as changes in the reactivity of the body with respect to adequate and inadequate stimuli are characteristic of acute polonium injury. Two principal periods may be distinguished -- the period of instability of the functional condition and the period of depression of the activity of the body. Functional changes in the central nervous system are comparable in time and apparently, to a considerable degree, produce changes in the other systems. Hereby, the direct effect of α-radiation of polonium on the tissues is of more than a little importance in the development of pathological process. During the period of the unstable state of the central nervous system considerable variations are observed in the blood pressure level, the magnitudes of the pressor effect in response to adrenalin, the respiratory gas exchange, etc. In the terminal period of radiation sickness the development of hypotension and a re-

duction in the oxidative processes are observed along with a depression of the central nervous system.

Analysis and the comparison of the experimental material make it possible to suppose that an important part in the disorders described is played by disturbances in the neuro-endocrine regulatory mechanisms. Unfortunately, the participation of the endocrine system has been little studied (R. A. Pigalev, A. I. Chuchukalo, V. M. Mastryukova, Leblond and Lacassagne). A change in the reactivity of the circulatory apparatus, the heat regulatory system, a disturbance in the regulation of carbohydrate metabolism, etc. are evidence of a disturbance in the regulatory mechanisms. It should be emphasized that it is possible to find a limitation of the adaptive possibilities of the irradiated organisms specifically in the study of the reactivity to various factors.

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The Effect of Total-Body X-Irradiation on the Excretion of Substances Determinable by the Dische Reaction in the Urine

(A Preliminary Report)

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In 1958 the work of a group of Czechoslovakian investigators (Parizek and others) was published in which it was shown that under the influence of total-body X-irradiation of white rats an increased excretion of substances determinable by the Dische reaction in the Stumpf modification is observed in the urine during the first 24 hours. By means of paper chromatography it was possible to establish the fact that the urine of irradiated rats contains desoxycytidine (conversion product of DNA), whereas in the urine of control rats this substance was not found. The greatest intensity of the stain in the Dische reaction with whole filtered urine and the greatest concentration of desoxycytidine in the urine were found with higher doses of radiation. In connection with this, desoxycytidine in the urine is regarded by the authors as an indicator of the changes following irradiation.

In the present report data are being presented concerning preliminary investigation of the excretion of the substances determinable by the Dische reaction in the urine and by concentrated sulphuric acid. In all, four series of experiments were performed. In each series there were six sexually mature male white rats weighing about 200 grams, two of which were irradiated with a dose of 600 r; two, in a dose of 200 r, and two rats served as controls. The conditions of the irradiation were the following: an RUM-11 apparatus, voltage of 180 kv, current 15 ma, filter 0.5 mm Cu and one mm Al; distance 40 centimeters; dose rate 32-25 r/min. Immediately after the irradiation the rats were put into three glass cages for the purpose of separate collection of the urine and stool for 24 hours during which time the animals were given only water. After 24 hours the collected urine was filtered through a paper filter, and the volume of it was measured. As a rule, in animals irradiated with a dose of 600 r the volume of urine was greater (on the average, 37.4 cubic centimeters) than in the animals irradi-

ated with a dose of 200 r (on the average, 24.1 cubic centimeters) and of the controls (on the average, 17 cubic centimeters), although the weight of the rats and the quantity of water consumed were the same.

For the purpose of comparison all portions of the urine were brought up to the volume of the maximum portion of urine with water, and the Dische reaction was performed in the Stumpf modification. Five-hundredths of a cubic centimeter of five percent freshly-prepared solution of cysteine hydrochloride, 0.5 cubic centimeter of urine and five cubic centimeters of 75 percent (by volume) sulfuric acid were poured into separate test tubes; these solutions were mixed with a glass rod, and after 50-60 minutes the absorption of light at a wave length of 490 millimu was measured using a Czechoslovakian K-56 spectrophotometer. Simultaneously, the reaction was performed with only 75 percent sulfuric acid without the addition of cysteine. In addition, the Dische reaction was performed also with urine treatment with activated charcoal. In Dische's opinion, substances which contain desoxyribose give a pink coloration with sulfuric acid with a maximum absorption at 490 millimu only in the presence of cysteine. Therefore, by determining the optic density of the stain obtained by the addition of cysteine and without the addition of it to a mixture of urine and 75 percent sulfuric acid it may be judged to what degree the pink coloration formed is brought about by substances containing desoxyribose. The spectrophotometric data are presented in the Table.

Spectrophotometric Results (Optic Density at 490 Millimu; Each Point Applies to Two Rats)

No. of Series	With Cysteine			Without Cysteine			Urine Treated with Activated Charcoal		
	Control	200 r	600 r	Control	200 r	600 r	Control	200 r	600 r
1	0,11	0,165	0,22	0,11	0,11	0,14	—	—	—
2	0,15	0,19	0,215	0,06	0,14	0,17	0,15	0,19	0,215
3	0,14	0,26	0,29	0,12	0,13	0,21	0,11	0,13	0,16
4	0,11	0,12	0,21	0,09	0,10	0,15	0,07	0,08	0,12
Average	0,13	0,184	0,232	0,095	0,12	0,167	0,107	0,133	0,165

In all four series it was found that irradiation

leads to an increased excretion of substances producing a pink color in the Dische reaction and in the reaction with concentrated sulfuric acid, whereby with a dose of 600 r the concentration of these substances is notably greater than after a dose of 200 r. A comparison of the data obtained shows that the absorption of light with a wave-length of 490 millimu after the addition of cysteine is greater than without the addition of it, but even without the addition of cysteine the absorption in the experiment is considerably greater than in the control. Evidently, the total-body irradiation of rats increases the excretion not only of substances containing desoxyribose in the urine during the first 24 hours but also of some other substances which do not contain desoxyribose. However, the dosage relationship is maintained in this case also. Treatment with activated charcoal reduces the degree of light absorption but does not eliminate the differences between the experiment and the control.

The data of our preliminary experiments confirm the results obtained by the Czechoslovakian investigators. At the same time, they indicate that after irradiation an increased excretion occurs not only of substances containing desoxyribose but also of some other substances producing a pink color with 75 percent sulfuric acid.

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Disturbance and Recovery of the Secretory Function of the Gastro-Intestinal Tract

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In the literature there are indications of a change in the secretory function of the digestive tract after radiation injuries (S. R. Perepelkin, M. F. Nesterin, Yu. N. Uspenskiy, K. V. Smirnov); however, it is not possible to find any data on the comparison of the disturbance in the secretory function of various divisions of the gastro-intestinal tract and the course of its recovery. Nevertheless, the elucidation of this problem is essential for developing methods of treating injuries of the digestive tract and, particularly, dietary therapy.

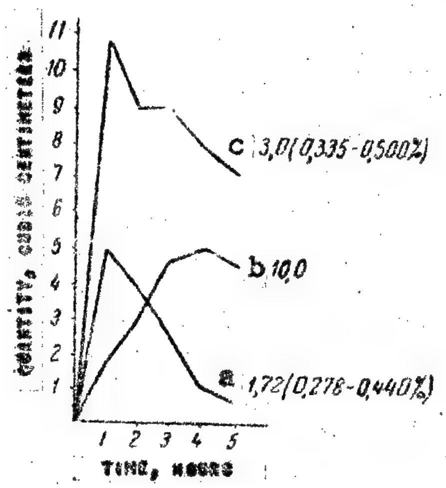
Experiments were performed on six dogs with isolated gastric pouches according to the method of Pavlov, with segments of the duodenum isolated according to the Thiry method and with isolated middle sections of the small intestine. The gastric juice was obtained in response to food stimuli for five hours. In the gastric juice the concentration of free and total acidity and the pepsin concentration (according to the Gross method) were determined. The intestinal juice was collected with a regular secretion for five hours; the intestinal enzymes were determined by quantitative methods accepted in the Institute of Nutrition of the Academy of Medical Sciences USSR. The concentration of enzymes was expressed in arbitrary units and applied to one gram of weight of the "mucous clumps" of the juice.

In dogs the initial level of secretion was established, after which they were exposed to a total-body single irradiation in a dose of 400 r under the following condition: voltage 180 kv, current 20 ma, filter 0.5 mm Cu and one mm Al; distance 90 centimeters; dose rate 15.4 r/min.

Ten to twelve days after irradiation a clinically expressed picture of radiation sickness developed in the dogs, which was characterized by sluggishness, loss of appetite, vomiting, diarrhea, loss of body weight, leukopenia. During theperiod of two to two and one-half months this condition alternated with periods of improvement, after which a clinical recovery occurred.

Change in the gastric excretion was expressed in the following. The latent period during the first three weeks

after irradiation was lengthened; following irradiation of the dogs the quantity of the gastric juice increased in the majority (after the administration of meat); in individual animals the increase in secretion alternated with a decrease in it. After irradiation secretion of gastric juice during the neural (first hour) and neuro-chemical (second-fifth hour) phases was modified, which was expressed in an increase or decrease in the absolute quantity of juice; however, in either case a predominance was found of the neuro-chemical phase of secretion over the reflex phase; this was expressed in an increase in the relative quantity of juice during the second phase compared with the first. With an increase in the excretion of the quantity of juice its acidity also increased. The concentration of pepsin during the first few days after irradiation increased somewhat regardless of the quantity of juice excreted. A typical example is presented in the Figure.



Secretion of Gastric Juice Before (a) and After (b,c) Irradiation. The Figures show the relationship of the quantity of juice P:1 phase and the content of free and total acidity.

In the study of the intestinal secretion it was noted that after irradiation the periodic character of the intestinal secretion was disturbed, and from time to time the secretion became continuous. In the juice secreted beginning with the 12th-16th day an admixture of blood appeared periodically. The quantity of juice beginning with the second week increased by several times compared with the original level, being replaced in the remote periods by a normal secretion. As early as the first few days after irradiation the concentration of certain enzymes in the intestinal juice (enterokinase, phosphatase) was disturbed considerably in the intestinal juice. The secretion of these enzymes decreased for the most part, although on individual days a considerable increase was noted in the concentration compared with the original level. A change in the intestinal secretion, which was of a wave-form character, lasted for several months; it occurred in segments of both the duodenum and of the jejunum.

Since certain authors (Warren, Whipple) on the

basis of their morphological data expressed the point of view that the intestine is more sensitive than the stomach to X-irradiation, it seemed interesting to compare the degree of change in the secretory function of the stomach and of the intestine and the time needed for its return to normal. In our experiment this was confirmed by the fact that changes in the intestinal secretion were more pronounced than those of the gastric secretion: after irradiation an admixture of blood appeared in the intestinal juice and was absent in the gastric juice; the concentration of enzymes (enterokinase, phosphatase) in various periods decreased considerably in the intestinal juice, whereas secretion of pepsin was practically unchanged (with the exception of a certain increase during the first few days after irradiation). For the purpose of recovery of the secretory function of various sections of the gastro-intestinal tract different periods of time were required -- first the secretion in the stomach returned to normal, and then that in the duodenum, and finally, that in the middle portion of the small intestine.

I. P. Pavlov, analyzing the work of the digestive glands, pointed out that "the more distal a digestive gland lies in the gastro-intestinal tract the less the participation of the neural apparatus in its activity...". Therefore, it may be considered that in our experiments the time for recovery of the disturbed secretory activity of various sections of the gastro-intestinal tract increased with a lessening of the connection of the given segment with the central nervous system.

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The Effect of Ascorbic Acid on the Carbohydrate Function of the Liver and the Survival Rate of Animals With Acute Radiation Sickness

V. S. Yusipov

The aim of the present work was a study of the influence of ascorbic acid on the carbohydrate function of the liver and the survival rate of animals depending on the time of its administration.

In experiments on 88 rabbits after a total-body irradiation with a dose of 500 r the effect of ascorbic acid was investigated on the sugar and lactic acid concentration in the blood, the nature of the sugar curves using a test with galactose. In the control group of experiments on 32 animals (after irradiation without the administration of vitamin C) it was established that the changes in the indices of carbohydrate metabolism in acute radiation sickness are of a phasic nature: the most marked changes are observed during the first few hours after irradiation; the changes are practically absent in the latent period, and recur during the period of the climax.

The administration of ascorbic acid before irradiation (in experiments on 25 rabbits) exerted an unfavorable effect. A greater increase in the concentration of lactic acid in the blood and an inversion of the shape of the sugar curves was observed hereby which was greater than in the control. In the experimental group, during the first two weeks after the irradiation, seven out of 25 animals died, whereas in the control group only three rabbits out of 32 animals died. The same harmful influence was exerted by vitamin C when it was administered immediately (one minute) after irradiation (in experiments on 12 rabbits).

In the next series of experiments (on 19 rabbits) ascorbic acid was administered 20 hours or later after the irradiation. Thereby, a distinct favorable influence of it was observed: the concentration of lactic acid in the blood (when investigated during the period of the climax of the sickness) became normal; the sugar curves assumed a shape similar to the original; and no deaths of animals were noted during the first two weeks after the irradiation.

In experiments on 70 white rats the effect of vitamin C was studied on the concentration of glycogen in the liver. The concentration of glycogen was determined by the Feulgen-Shabadash method and by the Pflüger method. Two hours after a total-body irradiation with a dose of 600 r the concentra-

tion of glycogen in the liver of the radiated animals proved to be higher (3489 milligrams percent) than in non-irradiated animals (1691 milligrams percent). We consider this increase of glycogen in the liver during the first few hours after irradiation one of the manifestations of the early protective reaction (glycogenogenesis through products of disordered metabolism).

The administration of ascorbic acid before irradiation inhibits this protective reaction, which is evidenced by the less pronounced (up to 2144 milligrams percent) accumulation of glycogen in the liver. The use of vitamin C during the period of five days before the irradiation, just as the single injection of it before irradiation, suppresses the protective reaction of the liver to irradiation. In the investigation three days after the irradiation the concentration of glycogen in the liver proved to be reduced to 746 milligrams percent. Still less glycogen (616 milligrams percent) was contained in the liver of animals which had been given vitamin C before irradiation. As a result of the administration of ascorbic acid one, two and three days after irradiation a considerable (by three and one-half times) increase in the glycogen concentration in the liver was noted (up to 2594 milligrams percent). The latter is evidence of the distinctly expressed favorable effect of vitamin C when administered after irradiation.

The data presented can contribute to an elucidation of certain problems of the pathogenesis of acute radiation sickness, particularly of the primary mechanisms of the effect of radiation on the body. A practical conclusion to be drawn from the results obtained should be the contraindication of the use of ascorbic acid for prophylaxis and immediate therapy of acute radiation sickness. Vitamin C can be recommended for the treatment of acute radiation sickness only after the disappearance of the signs of the primary reaction, that is, in the latent period and during the period of the climax. Here (within certain limits before irradiation) it is possible to contribute to a normalization of the metabolic processes by means of making up the vitamin C deficiency.

The Role of Ascorbic Acid in Radiation Sickness

V. S. Yusipov

There are still sparse and very contradictory data concerning the use of ascorbic acid in radiation sickness. Thus, after local roentgen therapy a favorable effect of ascorbic acid has been noted on the feeling of well being of patients, the antitoxic (V. S. Vladimirova) and the pigmentary function of the liver (K. S. Martirosov), the radiation leukopenia (Ellis), erythrocytopenia and thrombocytopenia (K. A. Skulme and L. Yu. Pranis). Under experimental conditions, after total-body irradiation of animals in sublethal and lethal doses, the favorable effect of ascorbic acid was not confirmed (Field and Rekers; Patt and co-workers; Horkykiewitsch and others). From the experiments presented in the article by Patt and his co-workers it is seen that the administration of ascorbic acid before irradiation of rats with a dose of 800 r exerted a distinctly harmful influence. Thus, while after irradiation without the administration of vitamin C 20 percent of the animals remained alive, after the administration of ascorbic acid before irradiation only 7-13 percent remained alive. Carrie and Schnetler noted a certain beneficial influence of vitamin C on radiation leukopenia when given to the animals before or after a total-body irradiation.

The contradictory nature of the results obtained by various authors is explained by the lack of unitypicality of the irradiation conditions and, therefore, of the form of radiation sickness, and by a difference in the time of administration of the ascorbic acid.

The discrepancy in the data in the literature dictates the need for further study of the mechanism of action of vitamin C and indicates the prematurity of unreserved recommendations on the use of ascorbic acid both for prophylaxis and treatment of radiation sickness (M. N. Pobedinskiy and others). In connection with this, it seemed expedient to us to elucidate the influence of ascorbic acid in different forms and stages of radiation sickness. A study was made of the effect of ascorbic acid on the course of the sickness and on the indices of the carbohydrate function of the liver.

The administration of ascorbic acid exerted a normalizing effect on the lactic acid concentration in the blood, which had been increased as a result of local roentgen therapy of patients. In experiments on 88 rabbits irradiated with a sublethal dose of X-rays the use of ascorbic

acid before irradiation and immediately after it exerted an unfavorable effect on the carbohydrate function of the liver and on the survival rate of the animals. On the other hand, as a result of the administration of ascorbic acid 20-24 hours after irradiation or later a distinct favorable effect of it was established on these indices. We obtained similar results in the determination of the glycogen concentration in the liver of rats irradiated with a dose of 600 r.

From all the observations presented here the data concerning the unfavorable effect of ascorbic acid when administered before irradiation or immediately after it are of particular interest. It would appear, by analogy with the protective use of cysteine, glutathione, etc., that it might be expected that ascorbic acid by reacting with peroxides should protect other biological substrates and primarily the reactive groups of proteins and enzymes. Ascorbic acid behaves in exactly this way _in vitro_ after the irradiation of a mixture of several organic substances. The introduction of ascorbic acid into the irradiated mixture exerts a distinctly protective effect which exceeds the protective effect of hyposulfite and cysteine (Anderson; G. Ye. Pavlovskaya and A. G. Pasynskiy; Ephraty; Loiseleur and others). It has been shown that ascorbic acid itself after irradiation _in vitro_ is oxidized in a considerably greater quantity than the other substances included in the mixture (Proctor and Goldblith). However, ascorbic acid contained in orange juice or muscles underwent a lesser degree of destruction than ascorbic acid in solution (Proctor and O'Meara, Anderson). This phenomenon can be associated with the fact that certain organic substances in their turn are capable of protecting ascorbic acid partially from the effect of radiation (N. M. Sisakyan).

The question arises: how are we to explain the harmful influence of ascorbic acid administered before radiation under conditions of the intact organism?

The data in the literature concerning the pronounced capacity of ascorbic acid (l-ascorbic acid) for oxidation after irradiation of it in solutions have been presented above. As is well known, in the oxidative destruction of ascorbic acid dehydroascorbic and diketogulonic acid as well as further decomposition products of it are formed. It is interesting to note that after irradiation of solutions the total quantity of l-ascorbic and dehydroascorbic acids decreases to a considerably lesser degree than the quantity of l-ascorbic acid alone, which is a direct proof of the formation of dehydroascorbic acid in irradiation; no 2, 3-ketogulonic acid was found (Proctor, O'Meara and others).

The capacity of ascorbic acid for undergoing vigorous oxidation, which has been shown in in vitro experiments (I. A. Serebrennikova and others), apparently occurs also after the irradiation of animals. The latter is confirmed in the abundance of data concerning the reduction in the volume of C concentration in the blood and tissues of the irradiated organism (L. Ya. Zhorno and many others). The reduction of ascorbic acid in this process is particularly marked during the first few minutes and hours after irradiation (V. S. Klimenko, K. A. Tret'yakova, Wexler) and in the most radiosensitive organs (Klein, Handa and Swick).

The formation of a considerable quantity of ascorbic acid oxidation products (principally dehydroascorbic acid) in the irradiated organism and the inactivation and acute deficiency of ascorbic acid which occur as the result of oxidation are of some consequence for the organism. Thus, in recent years it has been shown that the injection of dehydroascorbic acid (into rabbits in a dose of 1000 mg/kg and into rats in a dose of 70-100 milligrams per 100 grams) exerts a distinct toxic and diabetogenic effect (Patterson, Banerjee, Belavady, Mukherjee and others). According to the data of Mare Forti and Pece, the increased concentration of dehydroascorbic acid in the tissues inhibits the oxidative and energy processes in the animal organism. Ascorbic acid administered before irradiation can exert the same effect; it produces an increase in the quantity of dehydroascorbic acid formed, which is capable of intensifying the toxic effect of other inadequate substances, which are formed as the result of irradiation.

In addition, in acute vitamin C deficiency in the tissues of the irradiated organism blocks the links of metabolism of which the catalyst is ascorbic acid. Here, a disturbance in the nucleic acid metabolism is of the greatest importance. It is well known that the formation of nuclear desoxyribonucleic acid from ribonucleic acid occurs with the participation of ascorbic acid (B. Gol'shteyn and his co-workers). An acute inactivation of ascorbic acid after irradiation can be the direct cause of inhibition of the synthesis of desoxyribonucleic acid. It is characteristic that changes in the nucleic acids after irradiation are most pronounced in those tissues which contain more vitamin C: in the spleen, mucous membrane of the small intestine, etc. (R. G. Zaikina and others).

Definte importance is ascribed to disturbances in the nucleic acid metabolism in the pathogenesis of radiation sickness. It should be supposed that the interesting facts presented by V. I. Korogodin and G. G. Polikarpov are ex-

plained specifically by a disturbance in the formation of desoxyribonucleic acid from ribonucleic acid (with the obligatory participation of vitamin C in their metabolism). It has been shown that after the transfer of a non-irradiated nucleus to an irradiated cytoplasm reactions develop in the former which are characteristic of radiation injury, while when an irradiated nucleus is put into a non-irradiated cytoplasm no signs of injury can be detected (Duryee, 1947, 1949); subsequently, while the irradiated nuclei are capable of dividing in a non-irradiated ctyoplasm the non-irradiated nuclei do not divide in an irradiated cytoplasm (Harris and others).

Indirect confirmation of ascorbic acid inactivation from irradiation are the data of A. I. Strashinin concerning a reduction in the ascorbic acid excretion in the urine beginning as early as the second day after irradiation with a sublethal dose and the decrease in the capacity of assimilating administered ascorbic acid beginning with the fifth-seventh day after irradiation as well as the fact that symptoms characteristic of vitamin C deficiency are inherent in the period of the climax of radiation sickness (hemorrhagic tendency, reduction in the immune properties, stomatogingivitis and other dystrophic changes).

In connection with the possibility of the participation of ascorbic acid in the development of radiation sickness indicated the mechanism of action of prophylactic substances can be explained to a considerable degree by the protection of vitamin C against the effect of oxidizing radiolysis products (Bacq, Fischer) along with the protection of the reactive groups of proteins, etc. It is well known that the prophylactic substances have the common property of being antoxidants, regardless of their chemical nature (B. N. Tarusov).

The data presented cause us to wonder whether the particularly high degree of radiosensitivity of the hematopoietic, lymphoid tissue, hypophysis, suprarenals, sex glands, intestinal mucosa, lens, mitochondria, etc. is not associated with their considerable concentration of vitamin C, which exceeds the blood plasma ascorbic acid concentration by tens and hundreds of times (Giroud, L. M. Bremener and others).

Aside from the routes indicated there may be other routes of participation of ascorbic acid in the development of radiation sickness. Thus, ascorbic acid is necessary for synthesis of the suprarenal hormones the formation of which is considerably impaired in radiation sickness.

A practical conclusion to be drawn from the data pre-

sented should be that the use of ascorbic acid is contraindicated for the prophylaxis and immediate therapy of acute radiation sickness. Through the therapeutic use of ascorbic acid (after the disappearance of the signs of the primary reaction) we have established the existence of a favorable influence on the carbohydrate function of the liver and on the course of the sickness. This permits us to recommend the use of ascorbic acid for the treatment of acute radiation sickness in the latent period and the period of the climax. Evidently, within the limits of certain irradiation doses it is possible to contribute to a normalization of the metabolic processes by means of making up the ascorbic acid deficiency.

As has already been mentioned, ascorbic acid has a beneficial influence also in the mild form of subacute radiation sickness which develops during roentgeno-radiotherapy of patients.

The data presented attest to the participation of ascorbic acid in the complex mechanism of development of acute radiation sickness. The ascorbic acid changes in the irradiated organism can be the connecting link between the physico-chemical processes occurring as the result of radiolysis and the biochemical disturbances as well as other types of after-effect reactions. As is well known, specifically this link in the pathogenesis of radiation sickness remains one of the least studied. Clarification of the role of ascorbic acid in the pathogenesis of acute radiation sickness is one of the radiobiological problems for the immediate future. Essential aid in the accomplishment of this task will be given by finding methods which make it possible to determine the ascorbic acid oxidation products directly in the tissues of the intact organism.

Confirmation of the statements given concerning the role of ascorbic acid (naturally, taking into consideration the effect of the neurohumoral regulations) will make it possible to give a better grounded explanation of tissue radiosensitivity and of the intrinsic mechanisms of development of radiation sickness in place of the antiquated rule of Bergonie and Tribondeau and the Barron theory.

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CRITIQUE

Ye. D. Dubovyy. Radioactive Phosphorus in Therapeutic Practice (In Dermatology, Hematology, Surgery, Ophthalmology, Gycecology and Onccology). State Medical Press UkrSSR, Kiev, 1958, 213 pages.

The author has made it his aim to summarize the data existing in the literature and his own experience (more than 1100 observations) on the therapeutic use of radioactive phosphorus (P^{32}).

In the first small section of the book brief information is presented on the physical properties of P^{32}, its dosage, distribution in the body and excretion from the body. The second section is devoted to the use of P^{32} in diseases of the blood system (leukemia, polycythemia, multiple myeloma), skin diseases (angiomas, eczemas, neurodermatitis, psoriasis, mycosis fungoides, warts and certain others), surgical diseases (deep pyodermitis, furuncles, carbuncles, hydradenitis, thrombophlebitis and others), eye diseases (episcleritis, scleritis, keratoscleritis, pterygium, chalazion and others), pre-malignant conditions and malignant tumors (Bowen's disease, senile keratosis, skin carcinoma, erosions of the cervix uteri and others).

The book is well illustrated; specifically, mention may be made of Figures on colored inserts pertaining to the successful application of P^{32} in certain diseases of the eyes. There is a bibliography which includes Soviet works and a number of works of foreign authors on problems analyzed in the monograph. A clear-cut distribution of the material, a clear and lively presentation and a systematic discussion of the problems under analysis facilitate the reading of the book. The conclusions and deductions which the author makes, based on an analysis of the material in the literature and on his own data, are distinguished by definitiveness and conclusiveness of his evaluations. All this constitutes a positive characteristic of the publication being criticized.

An extensive group of treatment problems is touched on in the book, which are analyzed in connection with the evaluation of the significance of P^{32}, although not all the aspects of the problems under analysis are represented to the same degree in the monograph. Specifically, no place has been set apart for the use of radioactive chromium phosphate ($Cr\ P^{32}\ O_4$), particularly for radiosurgical purposes (Chevalier's method of gelatin films).

With respect to the principles of the therapeutic

application of P^{32} the author adheres to the correct attitude, in our point of view, of a moderate, as much as possible radiation effect and utilization of P^{32} in combination with other treatment measures. Thus, mention is made of the expediency of application of P^{32} in myelogenous and lympogenous leukemia in combination with blood transfusions, vitamin therapy and antibiotics. At the same time, this statement has not been supplemented by any explanations concerning the sequence of use of various agents in the comprehensive therapy, the dosages, etc. On page 44 a cursory comment is given concerning the expediency of combined use of P^{32} in certain cases with external roentgen or gamma-therapy in lymphogenous leukemia. In connection with this combination of treatment measures a more detailed discussion of the method might have been desired.

The author refrains from a comparative evaluation of the efficacy of application of P^{32} in chronic leukemias in view of the small number of patients treated and the inadequacy of the observation. Nevertheless, the problem of the significance of P^{32} in the arsenal of agents for the moderate treatment of leukemias is of profound interest to practicing physicians. Although this problem actually cannot be considered adequately clarified, an analysis of the existing data concerning the efficacy of treatment on a comparative plane would be of great importance. In this connection we may refer to the experience of 20 years of application of P^{32} for the therapy of leukemias, which made it possible for D. Lawrence to conclude that this method has advantages.

In the section devoted to the treatment of skin diseases material is presented and conclusions are drawn concerning the efficacy of treatment of capillary angiomas. On the basis of his experience the author gives recommendations concerning the technique of application in eczema and gives a foundation for the method of moderate single and total doses which he has worked out. Speaking about psoriasis he shows justified restraint with respect to the indications for the application of P^{32} in this disease, although the observation which he presents demonstrates the efficacy of the method. It should be stated that in describing applicators for external irradiation the author does not present any data concerning radioactive plastics containing P^{32}, which are of importance for the future development of this method.

In the section on surgical diseases the chapters devoted to the treatment of thrombophelebitis and inflammation (or strangulation) of hemorrhoids attract attention. Here,

interesting data are presented concerning the effectiveness of the treatment method worked out by the author and his co-workers. The description of the author's own experience in the field of application of P^{32} for the treatment of eye diseases is also read with interest. Ye. D. Dubovyy (in conjunction with S. F. Kal'fa, L. F. Voloshina and G. M. Zsygankova) worked out the application of P^{32} for the treatment of scleritis, keratitis, pterygium and chalazion for the first time in the Soviet Union. In the book data are reported concerning the method and the clinical aspects of this treatment, and descriptions of individual observations and colored illustrations are presented. It is shown convincingly that P^{32} extends the existing therapeutic possibilities in ophthalmology.

In the concluding section of the book a review is given, and certain data are presented pertaining to the application of P^{32} in pre-malignant staes and in malignant tumors. Here, an analysis is given on the results and perspectives of utilization of P^{32} for the treatment of hyperkeratoses and leucoplakias, cervical erosions and carcinoma of the skin. The advantage of application of P^{32} for the treatment of carcinoma of the lid is emphasized, and here the problem is pointedly posed of eliminating the radiation effect on the lens.

In characterizing the book being criticized as a whole it should be stated that the author undoubtedly has succeeded in accomplishing the task which he set before himself: generalizing the data of the therapeutic use of P^{32} at the current stage of development with the aim of further development and incorporation of this method into practice. Generalization of the data in the literature and of his own data has been accomplished by him with different degrees of completeness in different sections. However, the book gives the reader an idea of many general and specific problems. It has an advantage as a publication in which numerous scattered data have been assembled which apply to the utilization of P^{32} for therapeutic purposes. The author has been able to reflect, with a considerable degree of completeness, the achievements of Soviet authors and the recommendations worked out in the USSR in his book.

At the same time, the book is not without defects which are inevitable for the present first presentation of experience. Certain of them have been indicated above. We should like to mention our desire that the author continue his well-begun work, preparing a new edition of the book in which his own and collective multiple experiences will be reflected.

M. P. Domshlak

H. Jamet, G. Mathe, B. Pendic, J. F. Duplan, B. Maupin, R. Latarjet, D. Kalic, L. Schwarzenberg, Z. Djukic, J. Vigne.

Six Cases of Acute Radiation Sickness in Patients During a Nuclear Reactor Accident in Yugoslavia. Etude de six cas d'irradiation totale aigue accidentelle.

In the French journal, "Revue Francaise d'Etudes Cliniques et Biologiques" No 3 for this year three articles have been published in which the first scientific description is given of the nature of the injuries and the results of treatment of acute radiation sickness in six persons suffering from a nuclear reactor accident in Yugoslavia.

The editorial board of the journal "Meditsinskaya radiologiya" considers it expedient to give a detailed presentation of the material of recently published articles so as to acquaint our readers with data dealing with this illustrative case. In the world literature a few cases of acute radiation injury have been described in people. In this group there are two reports of Soviet (A. K. Gus'kova and G. D. Baysogolov) and American (Hasterlick and Marinelli) physicians at the First Geneva Conference on the Use of Atomic Energy for Peaceful Purposes and the well known monograph "The Radiation Syndrome" by Hempelmann.

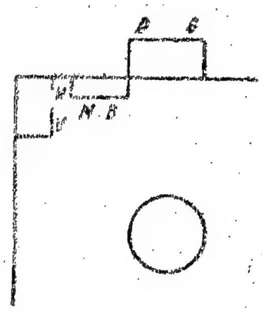

Fig. 1. Position of Those Affected in the Reactor Room (The Circle Designates the Reactor).

On 15 October 1958 an accident occurred in an experimental nuclear reactor, which usually functioned on zero power, at the Yugoslavian Institute of Nuclear Energy near Belgrade. The reactor, which operated on natural uranium, was filled with heavy water. The operation of the reactor could be stopped by means of cadmium rods. The reactor did not have a reflector or a protective casing. On the day of the accident there were six persons at a distance of four meters from the reactor. The positions of the workers are shown in Fig. 1.

The experiment consisted of measuring the neutron flux formed from the spontaneous disintegration and following the introduction of a source of neutrons in the form of a radium-beryllium mixture. As a result of the increase in the level of heavy water in the reactor and the introduction of a radium-beryllium source of neutrons the reaction went out of control. As a result the emanation of neutrons and γ-quanta occurred. The latter were emitted from the disintegration of short-lived fission

products in a nuclear reaction which proceeded according to the type (n, γ) as well as from the disintegration of radioactive isotopes formed from this reaction. The emission of neutrons lasted several minutes, and the emission of γ-rays lasted longer with a radioactivity decay characteristic of the radioactive isotopes formed.

From the very beginning the idea was gained that the patients had been irradiated in doses on the border of the lethal doses or even exceeding them. All six patients were sent to Paris the next day and put in the department of radiopathology of the Curie Institute. In the evaluation of the doses of radiation received the basic element consisted of physical measurements of induced radioactivity in the metal objects surrounding the reactor and in the bodies of the patients.

The total flux of thermal neutrons, determined by the activation of the metal objects, was equal to approximately $2 \cdot 10^{11}$ n/cm^2. The percentage of fast neutrons with a mean energy of 2.2 MeV amounted to six to eight percent of this value. It was assumed that the γ-radiation should be three times as much as the neutron radiation. Taking into consideration the time the patients had been in the reactor room and their positions in it, the dose of γ-rays was determined to be within limits of 450-1000 r (Table 1).

Table 1

INITIAL OF PATIENT	Na^{24}, MICROCURIES	DOSE OF NEUTRON RADIATION, REM	DOSE OF GAMMA-RADIATION, REM	TOTAL DOSE OF NEUTRON AND GAMMA-RADIATION, REM	EXTREME LIMIT OF GAMMA-RADIATION, REM	TOTAL DOSE, REM
V.	82	210	630	840	450—1 000	1 000—1 200
M.	75	214	642	856	450—1 000	700—1 000
G.	76	230	690	920	450—1 000	700—1 000
D.	63	256	768	1 024	450—1 000	700—1 000
H.	53	174	522	696	450—1 000	600—800
B.	45	102	306	408	250—500	300—500

The induced radioactivity in the bodies of the patients produced by Na^{24} was measured in Paris by means of a 45-channel γ-spectrometer. The values obtained for various people are given in microcuries in the second column of Table 1.

In the third column the dose of neutron irradiation is presented; in the fourth, the dose of gamma-irradiation found by multiplying the data in the third column by three. In the next column the calculated total dose is given for neutron and γ-radiation. However, this total dose should be considered as only approximate. As a matter of fact the

neutron irradiation was homogeneous, but the sources of γ-radiation in the room were many. For this reason the γ-ray field was not uniform in various places. In addition, the behavior of the various persons in the room was different: M., G., D. and H. remained relatively inactive after the accident. After three mimutes, B left the room; V. returned to the reactor after it had stopped, receiving an additional dose of γ-radiation. In the sixth column the limits of the possible γ-radiation are given, and in the seventh column, the most probable total dose for each patient taking into consideration all the facts. The subsequent clinical course of the injuries in general confirmed the estimation of the radiation dose given above.

The total-body irradiation caused in acute radiation syndrome corresponding to that described in the literature. During the first few hours after the irradiation the following were noted: asthenia, adynamia, psychic depression, anorexia, nausea, vomiting, paresthesias in the upper extremities and a tendency toward perspiration. In B., who had received less irradiation, there was no vomiting. V, the most severely irradiated, had diarrhea on the fourth day.

During the latent period, which lasted three days, the general condition of the injured persons was satisfactory, which was in contrast with the changes in the blood; in the injured person, V., a definite deterioration in his general condition was noted even during this period. On the 4th and 15th days this temperature rose. During the latent period the body weight dropped by 0.3-2.3 kg in the injured persons. During the period of the climax of the sickness, from the fourth through the seventh week after irradiation, a marked deterioration in the general condition occurred. With the exception of B., all suffered from fever. There was a loss of appetite, nausea appeared; there were profuse night sweats, and there was a reduction in diuresis (Table 2).

Symptomatic therapy as well as the administration of a bone marrow emulsion in four patients led to the fact that a gradual improvement was noted in the seventh week. V., the person irradiated most, died on the 32nd day during the climax of the sickness. B., who was not treated with the bone marrow transfusion recovered more slowly than the others.

On the first day erythema and conjunctivities developed in all those injured except B. The latter symptom was also observed in B. At the end of the second week a skin pigmentation was noted in the patients; in V., des-

quamation. In all the afflicted persons the hair of the head fell out, in B. beginning with the 14th day; in B., beginning with the 20th day. In the men (among the injured persons there was also one woman, D.) the hair of the beard also fell out. The epilation of the head was not uniform, which indicated different doses of irradiation of different parts of the head with the secondary γ-rays. The hair growth did not return before the third month. No changes were found in the lens; retinal edema was noted only in H.

Table 2

Initials of patients	Erythema	Conjunctivitis	Epilation	Weight dynamics, kg	Sperm changes	Complications
V.	++	++	Hair of head, 14th day	-2.3 8th day	+++	Abdominal pains, intestinal perforation, obstruction, anuria, terminal icterus
	1st day	1st day	Hair of beard, 14th day	-1.0 28th day		
M.	++	+	Hair of head 16th day	-1.6 6th day	+++	Abdominal pains
	1st day	1st day	Hair of beard 16th day	-3.0 118th day		
G.	+	+	Hair of head 18th day	-0.5 6th day	++	Abdominal pains, herpes
	1st day	1st day	Hair of beard 18th day	-6.2 18th day		
D.	+	+	Hair of head 14th day	-1.3 6th day		Abdominal pains, menstrual disturbances, herpes
	1st day	1st day		+9.0 120th day		
H.	+	+	Hair of head 17th day	-0.3 6th day	+++	Abdominal pains, subacute icterus partial obstruction

Table 2 [continued]

Initials of patients	Erythema	Conjunctivitis	Epilation	Weight dynamics,	Sperm changes	Complications
	1st day	1st day	Hair of beard 17th day	+5.6 106th day		
B.		+	Hair of head 20th day	+0.6 10th day		Abdominal pains
	0	1st day		-3.3 82nd day -2.6 120th day	+	

Peripheral blood analyses were made every two or three days in parallel in two laboratories. The blood picture before irradiation was normal in all. Only in D. was there a slight reduction in the erythrocyte and leukocyte counts. On the first day a leukocytosis developed (9000-11,000 per cubic millimeters); during the latent period the number of blood cells gradually decreased. The erythrocyte count decreased least; the lymphocytes, most. The lymphocyte count decreased to low levels during the first five days; afterwards, the variations occurred near the low level reached. The granulocyte count decreased even more slowly; at the end of the first and during the second week it increased somewhat. The number of platelets decreased to approximately the same degree as that of the granulocytes. The reticulocytes disappeared from the blood during the first two days after the irradiation. In Figs. 2 and 3 hemograms are presented for the entire observation period. During the third period of the sickness the blood picture indicated an almost complete bone marrow aplasia. The lymphocytes were maintained at the level reached at the end of the first week. The granulocytes passed through a minimum at the end of the fourth week. The neutrophils numbered a total of 50; only in B. did their number come up to 900. The platelet count dropped to 30,000. At the end of the fourth week the erythrocyte count decreased to 3,000,000; in B., to 4,000,000; in H. and D., to 2,200,000 and 1,400,000 respectively.

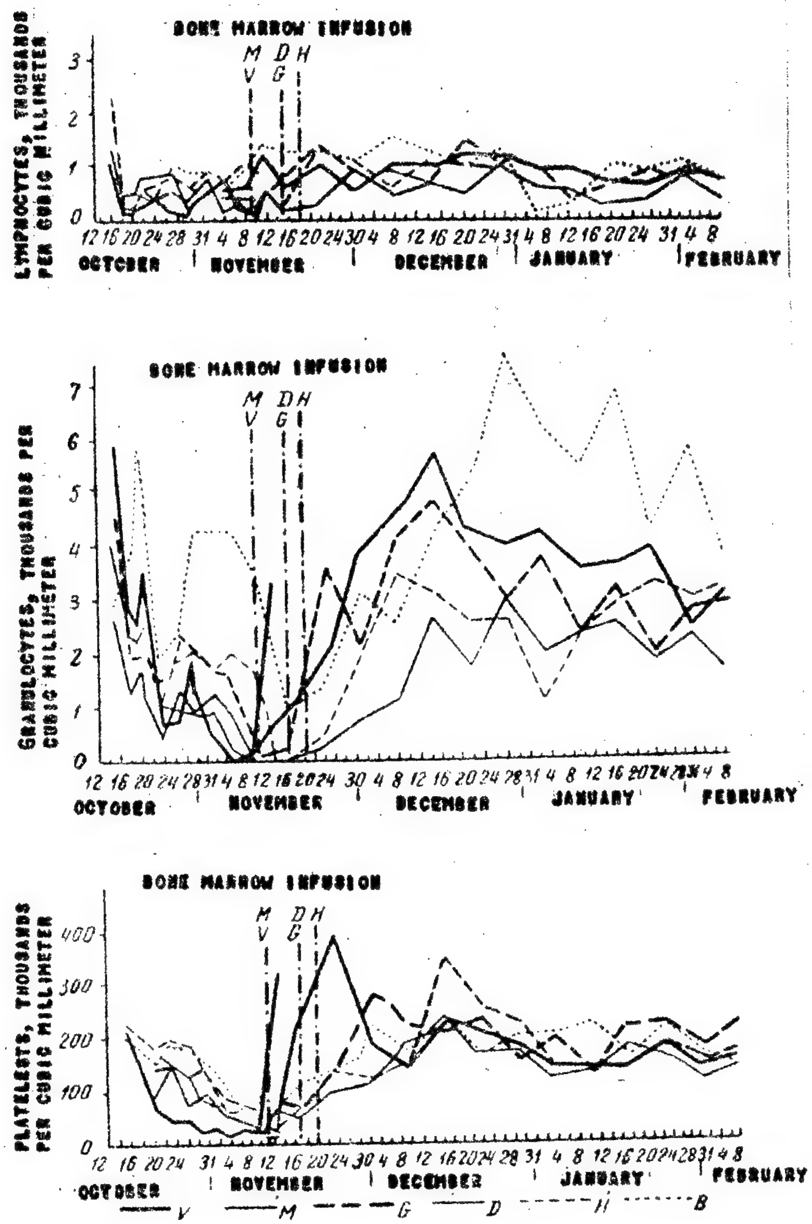

Fig. 2. Change in the Formed Blood Elements in the Patients

The bone marrow transfusion was given in the fifth week. In the next eight days the picture was substantially different. The platelet count increased by three times; the granulocyte count and reticulocyte count also increased. However, the lymphocyte count thereby did not change and varied with the same limits as before the bone marrow transfusion.

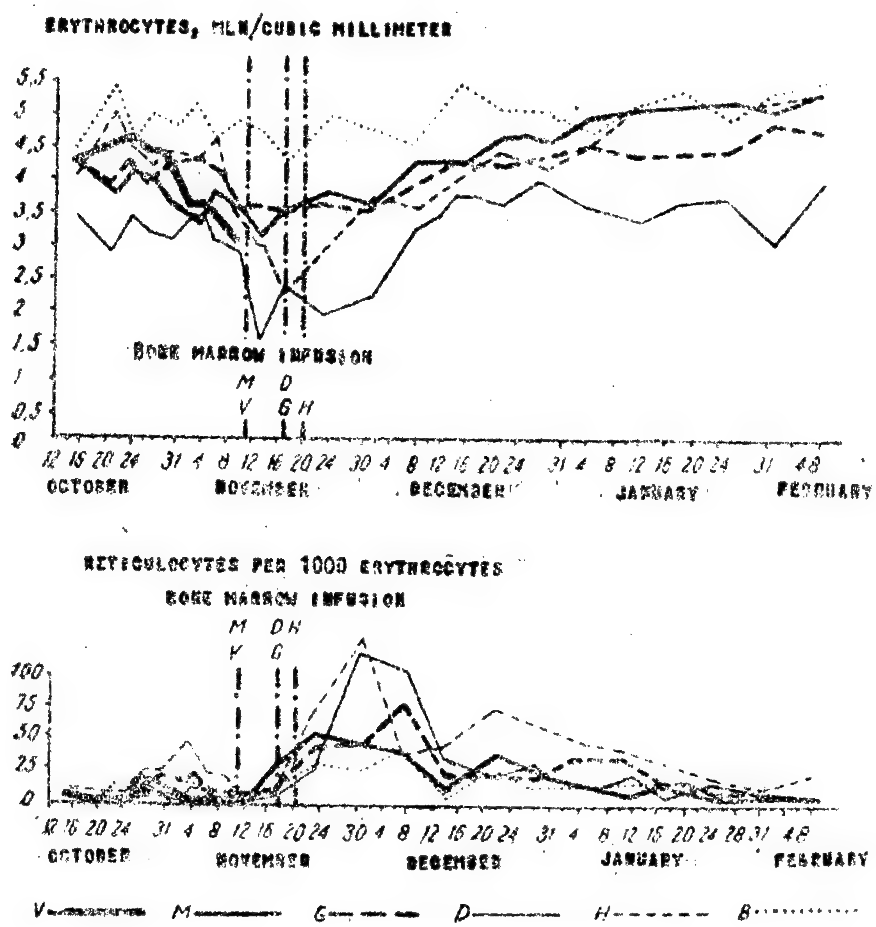

Fig. 3. Change in the Erythrocyte and Thrombocyte Composition of the Patients.

At the end of the second month the blood picture came close to normal, but was unstable. The lymphocytopenia was maintained. The phase of restoration of the blood was a consequence of bone marrow grafting and regeneration of the patient's marrow.

With respect to the white blood element the origin of the cells could not be determined -- whether from the donor's bone marrow or from the patient's. For the erythrocytes this could be established by the agglutination method. In B., who was not given any bone marrow, spontaneous recovery of the blood picture occurred slowly. An examination of the bone marrow was made every 10 days in the patients. During the first week a notable aplasia developed; at the end of the latent period it was complete. During the two weeks after the grafting the marrow "became populated," and the myelogram became almost normal.

Apart from the morphological examinations of the blood determinations were made of the blood coagulation and bleeding time, and analyses were made of the prothrombin complex; tests were made for hemoglobin tolerance, and thrombin-elastographic measurements, etc. were made.

The prothrombin complex was normal in all the patients except D. In D there was a reduction in the accelerin and proconvertin [accelerators of the prothrombin to thrombin transformation]. Thromboelastographic measurements were made every week, and considerable functional changes were shown. At the end of the latent period and during the crisis the coagulation time was definitely shortened and the amplitude was reduced. In N. these disturbances were particularly pronounced and were accompanied by purpura. The infusion of a thrombocytic mass reduced these signs. The hemorrhagic syndrome during the period of the crisis was manifested by hemorrhages from the gums. In D. and N. there were nasal hemorrhages. In N. purpura appeared in the lower extremities on the 26th day and did not disappear for two weeks. In D. there menorrhagia, which led to anemia. In V., who was the most irradiated person, intestinal and pulmonary hemorrhages were observed. Hematemesis and hemoptysis gradually increased in his case. At autopsy hemorrhages were found throughout the intestine; there was a pulmonary infarct and petechiae in the kidneys and urinary bladder. In patients M., G., D. and H. no particular disturbances were found in the heart or lungs, but the blood pressure was unstable.

The renal and liver symptomatology remained latent except in H., in whom there was a certain degree of icterus at the end of the period of the crisis. In all the patients at this time a disorder occurred in the activity of the gastrointestinal tract; there were disorders of the gum and cheek mucosal epithelium, diffuse pains in the abdomen, pains on palpation and peristaltic disturbances. In N. at the end of the period of the crisis there was a partial intestinal obstruction. In V. the complications of the internal organs were so severe that they caused his death on the 32nd day. He had intestinal obstruction, jaundice and anuria.

Examination of the sperm of the five men in the second week showed a reduction in the number of spermatozoa, and morphological and functional changes of them. On subsequent analyses no spermatozoa were found in two (M. and N.), and there were very few of them in G. and B. At autopsy in V. a complete evacuation of the seminiferous tubules was noted. In D. the menstrual cycle was disturbed, became ir-

regular, shortened; considerable menorrhagia occurred during the critical period, which coincided in time with the ordinary menstrual period.

In all the patients a quite detailed analysis was made of the biochemical changes in the blood and urine. The data are presented in Fig. 4. In general, no essential changes were found in the biochemical blood indices. The physical constants remained normal. The electrolyte balance underwent certain changes in the first week and during the period of the crisis: hypochloremia, hyponatremia, hyperkalemia. The total quantity of blood proteins decreased a little; the concentration of γ-globulin decreased, and sometimes there was an increase in the α- and β-globulins. During the first week, azotemia was observed at times.

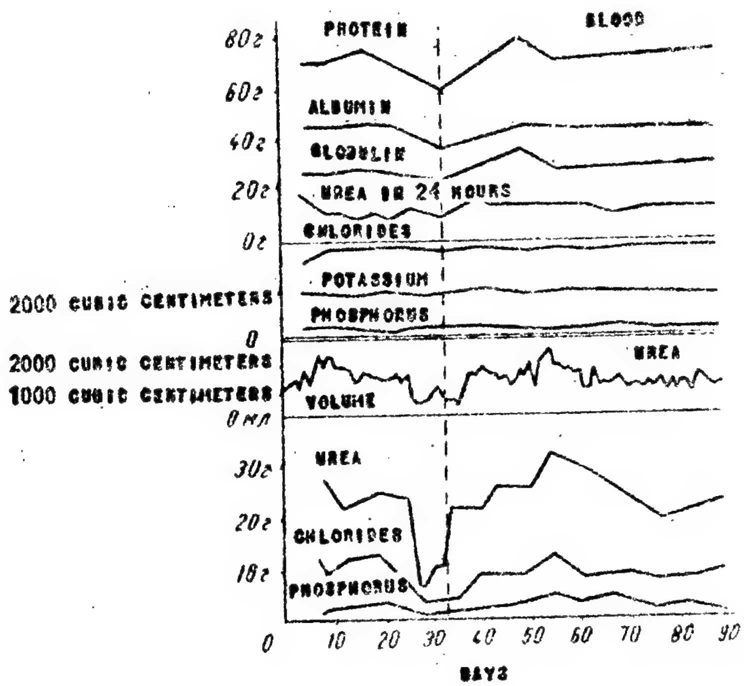

Fig. 4. Biochemical Changes in the Blood and Urine of the Patients.

The diuresis was very profuse (two to three liters per day) during the latent period. During the third period it decreased, and oliguria occurred. There was no glucosuria, but during the first two weeks albumin appeared in the urine. Urobilin and other pigments were found irregularly. It should be noted particularly that the amino acid nitrogen in the urine increased. Paper chromatography showed amino acids which are usually for urine as well as

those normally absent from it; proline, phenylalanine, tryptophane, threonine, aspartic acid. The amino acid recovery was particularly great during the first week but did not return to normal even afterwards. The functional tests for renal and hepatic activity did not show any changes in their condition. The sedimentation rate was elevated until the end of the critical period.

On the first day, before the patients were sent to Paris, they were given various agents to counteract shock and antibiotics. After their arrival at the Curie Institute the patients were kept under conditions of strict asepsis and antisepsis. No one was permitted to see them except nurses and physicians; antiseptics were sprayed. Complete rest was prescribed for them, but during the latent period the bed-rest routine was observed incompletely. From the third to the seventh week the patients remained in bed the entire time. During the latent period an ordinary hospital diet was prescribed. At the beginning of the period of the crisis the patients were transferred to a "hypotoxic" diet (composition unknown), and then to a special liquid diet (up to the eighth week). After the period of the crisis, they were gradually put back on the "hypotoxic" diet, and then the patients were transferred to the regular hospital diet. No recourse was had to parenteral feeding. Only patient V. was fed this way during the terminal period. Intense vitamin therapy was used: vitamins B, C, D, K, and PP.

Suprarenal cortical extracts and liver were injected regularly. Amino acids were administered, particularly, lobamine and cysteine.

Antibiotics were avoided until specific therapy was given. Afterwards, chiefly penicillin, streptomycin and terramycin were prescribed. Chloramphenicol was prescribed for gastrointestinal disorders. In Table 3 data are presented concerning the therapeutic measures.

Classic methods of treating hematopoietic disorders were utilized in a very limited manner. In order to compensate for the taking of blood for analyses, a transfusion of 150 cubic centimeters of whole blood was given on the third day. Patients N. and D, in whom anemia developed during the period of the crisis, were given an injection of erythrocyte masses. Massive infusions of isolated platelets were given to patients V. and D. (menorrhagia) and H. (purpura). Four patients were injected with γ-globulin during the latent and third periods.

Table 3

Initials of patients	Penicillin, units	Streptomycin, g	Terramycin, g	Chloramphenicol, g	Vitamins	Organ Therapy
V.	2,000,000 4th-15th day	1 4th-15th day	600-800 mg IM 22nd-32nd day	3 29th-32d day	Complex B,C, K,PP	Liver Extract, cortin
M.	2,000,000 22d-25th day	1 22d-25th day	600 26th-37th day 400 mg IM 24-40th day	3 29th-32nd day	Same	Lobamine Cysteine
G.		1 35th-38th day	2 g per os 84th-88th day	3 29th-33d day	Same	
D.	2,000,000 4th-13th day 4,000,000 27th-37th day	1 4th-13th day 1 27th-37th day	0	3 31st day	Same	Testosterone Progesterone
H.	4,000,000 51st-54th day	1 51st-54th day	600 mg IM 34-41st day 49-58th day	3 29th-32d day	Same	
B.	2,000,000 12th-19th day	1 12th-19th day	0	0	Same	

Because it was clear from the very beginning that in V. the course of the sickness was assuming a lethal character and that the same threat was being aimed at M. G., D. and H. the decision was made to infuse hematopoietic tissue. As the result of the danger of a secondary immune reaction following the infusion of adult tissue it was decided to administer embryonic hematopoietic tissue to V.; this was done on the 14th day (4,200,000,000 cells were injected).

The absence of the reaction to the injection and the further deterioration of the course of the sickness were the incentives for repeating the infusion on the 27th day. This time hematopoietic tissue was given which was taken from an adult donor by means of a bone puncture. The donor's phenotype was similar to that of the patient. Patient M. was given an infusion of homologous bone marrow on the 27th day; G. and D., on the 33d day; N., on the 36th. The number of cells administered was equal to 8,500,000,000 to 14,000,000,000 in a volume of 180-300 cubic centimeters. As was indicated previously, such infusions immediately led to a change in the peripheral blood picture in a favorable direction. Forty-eight hours after transfusion shock the patients' conditions improved, appetite returned, and they became more active; their feeling of well being improved, and their weights increased.

Patient B. was on the same routine as the others, receiving the same drugs and vitamins, but he was not given infusions of hematopoietic tissue. He recovered more slowly than the others despite the smaller dose of radiation.

On the basis of an analysis of the material collected the authors have drawn a general conclusion concerning all the aspects of the acute radiation syndrome problem. They direct attention to the difficulties which have to be overcome in determining the dose of irradiation, because the individual dosimeters were useless for such an accident. Evidently, in the case of an accident dosimeters with a range of γ-radiation doses of the order of 50-1000 r are needed.

In the clinical picture of the radiation injuries its early signs are very important: nausea, vomiting, diarrhea; we must direct attention to the skin changes and conjunctivitis. Epilation begins only during the period of the crisis. As far as the blood examinations are concerned, the relationship between the dose and the granulocyte counts are most pronounced; for lymphocytes and platelets the change in their counts with relationship to the dose is not so well-defined. Of the biochemical changes the most significant are the increase in the amino acid nitrogen concentration in the urine and the appearance of unusual amino acids in the urine.

These cases are instructive in connection with the fact that in B., who was irradiated with a dose of less than 500 rem, the recovery in the general condition and blood picture occurred slowly. This, however, does not mean that with this dose it was necessary to resort to a dangerous manipulation -- the administration of hematopoietic tissue. In

patients M., G., D. and H. in whom the dose was greater than 500 rem, the ordinary treatment was inadequate. The administration of hematopoietic tissue in this case gave the patient's body the time for recovery of his own myeloid tissue, which is essential for survival. The selection of the time for administering the hematopoietic tissue depends on the knowledge of the dose received. The onset of the period of crisis, at which time the clinical course may confirm the dosimetric data, is convenient. However, in this case, as with V., the administration of hematopoietic tissue should be given as soon as possible.

With respect to the prognosis the authors have come to the following conclusion. The possibility of a secondary immunological reaction in those given bone marrow injections cannot be excluded. As immediate complications abnormalities in the blood picture, abnormalities of spermatogenesis, asthenia are possible; as remote consequences, the increased probability of leukemia and various kinds of carcinoma.

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END